GRUBER FOUNDATION

Shigetada Nakanishi: Narrative Biography

The recipient of the 2007 Gruber Prize for Neuroscience is transforming our understanding of the workings of the brain and nervous system. It's not the career his parents had in mind, but this quiet achiever is attracting international attention.

Times were tough in Japan immediately after the Second World War, and in the small rural city of Ogaki, northwest of Nagoya, the parents of the young Shigetada Nakanishi found life more difficult than most. As a result, they became determined that their son would make a difference, would become a useful person.

That's why they were initially somewhat disappointed when, after earning his degree in medicine, Nakanishi didn't open a medical practice.

Instead he turned to a PhD in biochemistry and a life of research. "I found myself wanting to know the logical explanation for clinical treatments. At the time it was difficult to explain the mechanism of many diseases and the actions of the drugs used to treat them. I wanted to understand biological systems at a molecular level."

Forty years on, no one can deny that the recipient of the 2007 Gruber Prize in Neuroscience has made a difference. Now director of the Osaka Bioscience Institute, Professor Shigetada Nakanishi has pioneered the area of communication between nerve cells in the brain. He and his research team have unraveled much of the molecular detail of information transfer and processing. And his work has provided pharmacologists with many new possibilities for drug design.

"A full understanding of the workings of the human brain is still decades or more away," according to Richard W. Tsien, a member of the Gruber Foundation's Neuroscience Advisory Board.

"But Shigetada Nakanishi's work is bringing it closer. He is an unusual researcher who has both created sophisticated tools to help us investigate the brain, and used these tools to make remarkable discoveries about the molecular processes used throughout the nervous system: our senses, movement control, cognition, learning, memory and much more," says Tsien.

It was during his medical training at Kyoto University that Nakanishi first became interested in how the body was integrated, how information was transmitted between cells and organs. Clearly, the center of this activity was the brain and, where most researchers would have been intimidated by its complexity, Nakanishi simply became fascinated. He decided he wanted to explore the molecular mechanisms of brain function.

Communication between nerve cells depends on chemical compounds known as transmitter substances. When an electrical impulse reaches the end of a nerve fiber it stimulates the release of these compounds, which move across the small gap to another fiber and bind to receptors there. This action either encourages or discourages firing of the second nerve fiber. Nakanishi soon became familiar with the major elements of this process in the brain—the neurotransmitter substances which can excite or inhibit depending on their structure and the receptors to which they bind. But he also became aware of a huge range of other compounds that can regulate or modify the process in subtle ways. And behind the whole system stood the genes that encode the information from which all these compounds are produced.

To increase his knowledge base, in 1971 he went as a postdoctoral fellow to the National Cancer Institute of the US National Institutes of Health in Bethesda, Maryland. It was just at the time that recombinant DNA technology was being developed. "I became extremely excited," he says.

He began applying those new techniques in a study of the small amino-acid chains or peptides that act as hormones and transmitter substances targeting the nerve cells in the brain and throughout

Shigetada Nakanishi in the labaratory with members of his research team

the body. What he found was that one peptide encoded by a single gene could subsequently be split in cells into multiple regulatory hormones.

Using his new techniques after his return to Kyoto in 1974, he similarly discovered several families of transmitter substances, a bewildering diversity of more than 50 compounds with different functions. He guessed there would be an equivalent diversity of receptors to which these transmitters bound. But while techniques existed to isolate and purify the individual transmitter substances, it was difficult to do the same with receptors, which were an integral part of the cell membrane.

The breakthrough came when Nakanishi developed a novel technique for purifying and cloning individual receptors in the egg cells of the African clawed frog, Xenopus laevis. He constructed a complementary DNA (cDNA) library comprising messenger RNA (mRNA) sequences of the brain and injected it into frog egg cells. An mRNA sequence that encoded a receptor would be processed in the frog cell, and the protein-based receptor it produced would become incorporated into the membrane. It would then respond to a small electric current. This effectively disclosed its presence, and the cDNA responsible could be tracked down by identifying increased levels of the same response in fractions of the cDNA mixture.

Using his technique for cloning receptors, Nakanishi and his research team spent many years studying nerve receptors and their interactions with transmitter substances. He was particularly interested in the diversity of receptors associated with the body's most widespread excitatory transmitter substance—the amino acid glutamate. He cloned and elucidated two broad groups of glutamate receptors—ionotropic, in which the receptor directly controls the opening and closing of pores in the membrane through which ions can pass; and metabotropic, in which the receptor exerts its impact by controlling signaling cascades inside the cell.

"Identifying the molecules involved in brain function greatly helps to solve the question of how information is transmitted and regulated and the integration and processing of information," Nakanishi says. But he also wanted answers to the question of how nerve cells, transmitters and receptors formed neural networks, the link between different nerve cell types and the receptors they used, and why there were so many different types of receptors. So he used multidisciplinary approaches such as gene targeting, pharmacology, and electrophysiology, and he addressed the processing systems that handle the information gathered by sensory organs, such as the eyes and nose. For example, he found the visual processing system, which used a common transmitter of glutamate, had different types of receptors responding to dark and light. Nakanishi and his team also investigated memory formation and motor coordination.

"But such approaches are not sufficient for pursuing mechanisms underlying integrative brain function and dysfunction," Nakanishi says. For that quest, he developed another technique, originally exploited in cancer therapy by the man in whose laboratory he worked at NIH, Ira Pastan. Known as cell ablation, it was a means of knocking out specific cancer types which use a particular receptor. Pastan generated antibodies which attached only to that receptor, and carried a toxin to kill the cancer cells carrying it. Collaborating with Pastan, Nakanishi extended this technique to neuroscience and used it to disable all the different nerve cell types in a neural network in turn. The information gained can disclose integrative mechanisms of brain function as well as compensatory mechanisms of brain dysfunction.

Many drugs have their effect by binding to receptors. So Nakanishi's work in identifying and purifying receptors has been of immense interest to the pharmaceutical industry. Once we know the structure and function of a receptor, it can become a target for drugs designed to stimulate or block it. One set of glutamate receptors in particular, N-methyl-D-aspartate (NMDA) receptors, are associated with not only memory and learning, but also with apoptosis or cell suicide in nerve cells. These have come under special scrutiny.

Nakanishi's work has been highly acclaimed over the years. His papers are some of the most widely cited in neuroscience. In 1995 he won the Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience Research, and the next year shared the Keio Medical Science Prize with Nobel Laureate Stanley Prusiner. He was elected to the US National Academy of Sciences in 2000 and became a Person of Cultural Merit in Japan last year.

His parents can be well proud of how useful their son turned out to be.

Written by Tim Thwaites and Niall Byrne, Science in Public, 28 June 2007

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