



BALDOMERO M. OLIVERA: Pushing the frontiers of neuroscience through venomous marine snails

by Karl Cabalteja

The human brain, arguably the most complex and intricate structure in Nature, has yet to be fully understood. A biochemist by training, Dr. Olivera has been instrumental in pushing the frontiers of neuroscience research forward with his work on venomous cone snails. Dr. Baldomero M. Olivera is a distinguished scientist in the fields of molluscan biodiversity, toxicology, and neuropharmacology, with over 280 publications to his credit. *Toto*, as he is fondly called, has spent the past three decades working on conotoxins, neuroactive peptides produced by the marine snails of the *Conus* genus, thus allowing the elucidation of key molecular mechanisms in the function of the nervous system.

The beginnings of Dr. Olivera's career as a scientist can be traced back to the University of the Philippines. He pursued a major in chemistry, later on graduating *summa cum laude* and valedictorian of UP Class 1960. Afterwards, he was awarded a Fullbright scholarship, through which he pursued his doctorate degree in biophysical chemistry at the California Institute of Technology in Pasadena under the tutelage of Dr. Norman Davidson. He then obtained his

post-doctoral degree in biochemistry at Stanford University in Palo Alto under Dr. Robert Lehman. In 2008, he was awarded Doctor of Science, *honoris causa*, by the University of the Philippines.

Although most famous for his work on conotoxins, Dr. Olivera's initial research had little to do with them but rather revolved around the properties of the then-newly discovered DNA molecule. At Caltech, he published his first papers on the biophysical characteristics of DNA including the electrophoretic properties of nucleic acids. Later on, during his post-doctoral studies at Stanford, he further immersed himself in DNA research, eventually becoming involved in the discovery of the nucleotide-joining enzyme DNA ligase from *E. coli*, a significant scientific discovery which helped pave the way for the development of molecular cloning techniques. He then went on to publish several more papers regarding the mechanism of DNA replication and pyridine metabolism.

His research on cone snails started soon after he finished his post-doctoral studies. He returned to the Philippines with the knowledge of the latest techniques in molecular biology, hoping to work further on



Left: *Conus geographus*, the first of the cone snails to be studied by Dr. Olivera, was named because of the map-like markings on its shell.

(Photo credit: Kerry Matz, <http://publications.nigms.nih.gov/findings/sept02/snails.html>)

Right: *Conus magus*, the cone snail from which the painkiller drug ziconotide was derived.

(Photo credit: CONCO: The Cone Snail Genome Project for Health <http://www.conco.eu/summary.html>)

characterizing DNA ligase. His laboratory, however, lacked sufficient funds to pursue such research. Thus, Dr. Olivera set his sight upon research which did not require sophisticated equipment: determining the lethal component of sea shells, such as *Conus geographus*, that he used to collect as a young boy. This initial foray into cone snail research resulted in the isolation and purification of the first of the conotoxins.

Conotoxins are neuroactive peptides composed of 10 to 30 amino acids, typically containing one or more disulfide bonds. These peptides are highly selective; they are capable of discriminating between ion channels which are highly similar. This characteristic of conotoxins has made them indispensable tools in neurophysiology, specifically, in the study of the structure and function of the many types and subtypes of ion channels. It has also made them prime drug candidates for several disease states, such as intractable pain. Indeed, one of the earliest conotoxins isolated by Dr. Olivera's team, omega-conotoxin MVIIA from *Conus magus* (synthetic version known as ziconotide) has been approved for clinical use by the FDA. Ziconotide was shown to be more potent than morphine as an analgesic, and unlike morphine, it does not induce the development of tolerance, thus, making it suitable for the treatment of chronic pain. Ziconotide is also known as Prialt™ or Primary Alternative to morphine.

Dr. Olivera's impressive research on both DNA biophysics and conotoxins has enabled him to serve as an

editorial board member of various scientific publications. He served as a member of the editorial board of the *Journal of Biological Chemistry* from 1982 to 1987, the *Journal of Toxicology – Toxin Reviews* from 1990 to 1993, and *Toxicon* from 2000 until the present. In addition, he was a member of the review committee of the journal *Cellular and Molecular Basis of Disease* from 1982 to 1986. Dr. Olivera has also served as a member of advisory committees of various institutions. He was a member of the Visiting Committee of the Department of Molecular Biology and Biochemistry of Harvard University from 1988 to 1995, the Advisory Committee to the Director of the National Institutes of Health from 1996 to 1999, and the Toxicology Advisory Committee of the Burroughs-Wellcome Foundation from 1999 to 2001.

Dr. Olivera has held various teaching positions in prestigious universities after obtaining his post-doctorate degree. His first teaching post was in the Department of Biochemistry of the College of Medicine at University of the Philippines, where he held the position of Research Associate Professor of Biochemistry. Currently, he is a Distinguished Professor of Biology at the University of Utah, and an Adjunct Professor at the Salk Institute in La Jolla, California and the Marine Science Institute at the University of the Philippines.

Throughout his scientific career, Dr. Olivera has garnered numerous awards and honors from various institutions recognizing his excellence. He has been a

Damon Runyon Fellow, a recipient of the *Ten Outstanding Young Men of the Philippines* Award; he has received the Eli Lilly Unrestricted Research Award, the American Cancer Society Faculty Research Award, the Alexander van Humboldt Foundation Senior Scientist Award, and the Utah Governor's Medal for Science and Technology. He was awarded as California Institute of Technology Distinguished Alumnus in 2002 and the Redi Award by the International Society for Toxinology in 2003. In 2005, he was elected to the US National Institute of Medicine.

In 2006, he won a four-year \$1 million award for a biodiversity-biomedical links education initiative as one of 20 new "Million-Dollar Professors" named by the prestigious Howard Hughes Medical Institute. In 2007, he was named 2007 Scientist of the Year by the Harvard Foundation for his "Outstanding Achievements and Contributions to American Science" and he was elected member of the American Academy of Arts and Sciences and the American Philosophical Society. In 2008, Dr. Olivera was awarded the Philippine Legion of Honor Presidential Award (Rank of Grand Officer) by President Gloria Macapagal-Arroyo in recognition of his significant

achievements and contributions in the field of marine science. Dr. Olivera is a Corresponding Member of the Philippine National Academy of Science and Technology. In 2009, he became the first Filipino to be elected to the US National Academy of Sciences.

Even with his international stature and success, Dr. Olivera remains one of the most ardent proponents of the development of science in the Philippines. In the last thirty years, he has consistently provided training opportunities for Filipino researchers in his laboratory at the University of Utah, with many researchers earning their graduate degrees with work on venomous marine snails. More recently, he has pushed new frontiers of exploration of marine molluscan biodiversity in the Philippines by his contributions to the conceptual framework and implementation of two major programs known as the PharmaSeas Marine Drug Discovery Program funded by the Philippine government and the Philippine Mollusk Symbiont-International Biodiversity Cooperative Group program funded by the US National Institutes of Health, US National Science Foundation and the US Department of Energy.