The Cone Snail that Delivered the Golden Goose

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When I started to write this essay, I was reminded of the fable about "The Goose that Laid the Golden Eggs". In one version of the story, a goose that laid one egg everyday was killed by a farmer thinking that there were a lot of golden eggs inside. When opened, the goose proved to be like any normal goose without any gold.

In "The Cone Snail that Delivered the Golden Goose" let me share with you the story about the basic research on cone snails undertaken by Dr. Lourdes J. Cruz of the University of the Philippines, and Dr. Baldomero M. Olivera, Dr. J. Michael McIntosh, and Craig Clark (in memoriam) of the University of Utah. Their research led to the team's recognition as 2022 Golden Goose Awardees under the stewardship of the American Association for the Advancement of Science. The Golden Goose Award is a United States award that is conferred in recognition of scientists with seemingly obscure, federally funded basic research that led to major breakthroughs resulting in innovation or invention with significant impact on humanity.

Cruz was a faculty member at the Department of Biochemistry (now Department of Biochemistry and Molecular Biology), U.P. Manila. Olivera was a faculty member in the same department while he also worked on DNA synthesis at Kansas State University. Dr. Olivera was, in fact, one of the researchers who discovered DNA ligase, an enzyme used in DNA replication and repair. In the 1970s, research in the Philippines was hindered by inadequacy of equipment, so Cruz and Olivera embarked on the cone snail project.

Cone snails (genus *Conus*) abound in the country, counting about 750 species. Hence, with limited equipment, Cruz and Olivera started investigating the nature of cone snail venoms. The cone snail hunts prey in various ways, and they have specialized diets. There are those that eat worms, others eat mollusks, and the rest eat fish. The cone snail immobilizes a fast-moving fish prey by using a highly specialized venom apparatus. To catch a fish, a usual strategy is for a cone snail to bury itself in the sand and extend its proboscis that is like a fishing line. The cone snail injects venom into the prey by means of a disposable hollow tooth, which serves as a hypodermic needle and harpoon. When the tip of the proboscis touches the fish, the snail ejects the needle-like structure from the end of the proboscis and harpoons the fish, allowing paralytic venom to flow through the hollow proboscis. As the fish prey has been paralyzed, it is swallowed whole by the cone snail. Because of the potent venoms, the cone snails, particularly the geography cone *Conus geographus*, have caused fatalities in humans. An early discovery of the cone snail team involved the nature of the venom. The researchers discovered that the bioactive venom components were small proteins known as peptides which were named conotoxins or conopeptides.

Olivera moved to the Department of Biology (now School of Biological Sciences), University of Utah, while Cruz collaborated with him initially via long-distance communications and later obtained a research faculty position that allowed her to visit the University of Utah periodically. The laboratories at U.P. Manila and U.P. Diliman Marine Science Institute (where Cruz later became affiliated) provided crude venoms from various cone snail species, while the University of Utah provided access to cutting-edge technology used for venom analyses.

Craig Clark and J. Michael McIntosh, undergraduate biology students at the University of Utah, later joined the team. Clark was specifically curious about the brain leading him to discover the technique that altered the course of cone snail research. Initially, different venom components were injected into the muscle of laboratory mice, but nothing noteworthy was observed. Then Clark experimented to find out the effects if the venom were injected into the brain of mice. He did cranial injections, and the results were astonishing – a range of behavioral effects in mice were seen. Different venom fractions caused hyperactivity, circular motion, scratching, depressed activity, sleep, back legs drag, paralysis, convulsion, coma, etc. Thus, each venom component was hypothesized to target highly specific areas in the brain. McIntosh joined the team after the laboratory started using Clark's brain injection method. In 1987, Olivera, Cruz and McIntosh, along with other collaborators, published in SCIE-indexed journal *Biochemistry* the purification from the magician's cone *Conus magus* (a fish-eating species) of a venom component that caused shaking in mice. The peptide referred to as omega-conotoxin MVIIA consists of 25 amino acids. The team proved that omega-conotoxins blocked calcium channels. With other collaborators, they discovered other omega-conotoxins that are useful in the elucidation of how the body transmits signals to the brain.

Several years later, the discovery led to the development of omega-conotoxin MVIIA into a potent pain reliever named ziconotide that is commercially known as Prialt. It is noteworthy that ziconotide is a complete synthetic copy of omega-conotoxin MVIIA that is much more potent than morphine but does not develop tolerance or cause addiction. Patients who use Prialt are equipped with a programmable and refillable pump that is implanted into the abdominal cavity and needs to be refilled every few months. While this procedure inevitably limits the use of Prialt, the medication can be used as an alternative treatment to morphine. This option has been life-changing for the patients who use it, particularly those who are suffering from cancer, AIDS, or other chronic conditions and are unable to cope with severe pain.

Due to their ability to cause specific behavioral effects in pre-clinical models, the omega-conotoxins have been useful to researchers in the development of novel methods to map the nervous system. With omega-conotoxins as probes, neuroscientists are mapping the brain's calcium channels. Over the years, several other types of conotoxins have been discovered, including conantokin whose name was derived from the Filipino word "*antokin*" because it causes sleep when injected into the brain of young mice. Many of those conotoxins were found to influence neurotransmission. Thus, scientists are exploring the possibility of using the omega-conotoxins, conantokins, and the other types of conotoxins to treat various brain disorders.

Sadly, Clark passed away at a young age. His concept of injecting venom into the brain of mice has brought a lot of benefits to humans through its important applications in neuroscience and medicine. The curiosity, innovation and serendipity proved to be very remarkable in the cone snail research.

Unlike the goose, the cone snail needed to be 'sacrificed' (killed) to obtain the 'gold mine' that comprises the various types of conotoxins. Thus far, the conotoxins have proven to be beneficial to humanity. Also, the cone snail has successfully delivered the Golden Goose to the highly deserving scientists.

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