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From Predator to Savior*

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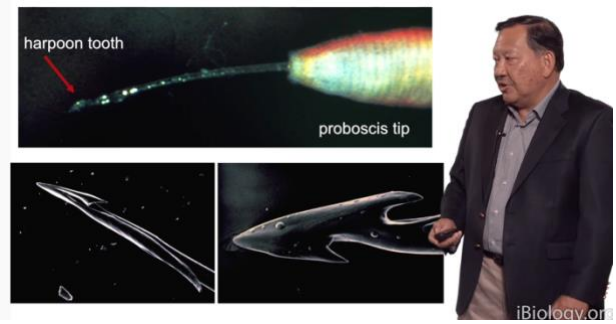
Story goes one summer in the seventies, Dr. Baldonado Olivera was watching predatory cone snails prance around in his aquarium at his summer home in the Philippines when he had an aha moment. When Toto saw those *Conus* snails a light bulb lit up and he came up with a new research topic to pursue in his lab in the Philippines. How exactly does the venom work on its prey when the harpoon like part of the snails stick out and squirt them out? What in this venom paralyze the tiny fishes and even fellow snails that give the predator snail time to eat them up, even leisurely at times?



See how it stings at 25:05
https://m.youtube.com/watch?v=Y5Ubr-sgUGw

Toto, as he is popularly known, splits his time between the University of Utah and the University of the Philippines, Padre Faura during his career as a biochemist. This curiosity of his is no surprise. Biochemistry is his passion. After Dr. Olivera graduated from the University of the Philippines with a BS in Chemistry he switched his interest from molecules and atoms to bioplymers particularly DNA. He went on to obtain his PhD in Biochemistry at Caltech and did his postdoc in Biochemistry at Stanford.

After that summer, he went back to the University of Utah where he was a Professor of Biochemistry and continued his new project, The Study of the *Conus Magus*, a type of predatory cone snails. He was a resourceful mentor giving opportunities to young students interested to do research in his lab. He decided to give a student straight from high school, J. Michael McIntosh, a labor intensive summer project. The incoming freshman was to isolate the key component(s) that is responsible for the lethal property of the venom. Mcintosh turned out to be a stellar budding scientist. He not only isolated the component(s), which turned out to be a mixture of polypeptides, but he also characterized the structure of an important one now known as ziconotide.

Ziconotide is a polypeptide consisting of 25 amino acids strung together like beads, not long but very powerful.

H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH2

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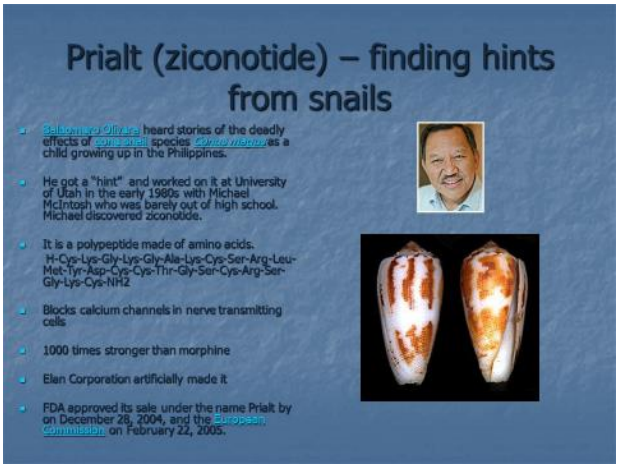
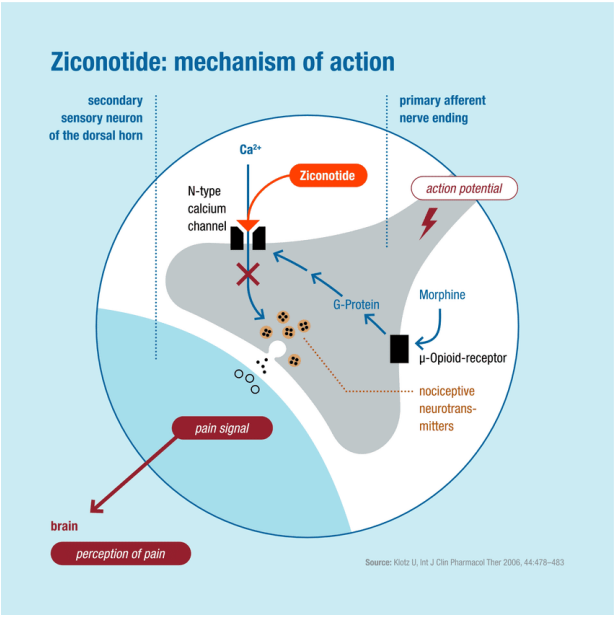


Olivera's group got involved in molecular neuroscience using the *Conus* venom components as a vehicle to investigate the function of individual ion channels and receptors. With the Ziconotide isolated on hand, Olivera, started to delve into the mechanism behind its action. He found that it is a calcium channel blocker in the nerves transmitting cells. Without the calcium ion the transmitters fail to relay the pain message or signal to the brain.

When Toto and collaborators were working early on Ziconotide, they did not have a definite therapeutic use for it and did not file a patent. They published the structure of this polypeptide which gave another group the idea to synthesize it in the lab with chemicals. This group filed a patent and distributed it as a new pain killer. It is 1000 times more potent than morphine and not addictive and has no withdrawal symptoms. It does not cross the blood brain barrier and cannot be taken orally but need to be injected into the spine.

Olivera studied several polypeptides from conus venoms and submitted them for human clinical trials. In 2005, Ziconotide (now known as Prialt) was approved for the treatment of intractable pain.



Curiosity they say kills a cat. But if it originates in a brilliant mind like Toto Olivera it kills the pain of hundreds of patients for whom opioids like morphine fail to relieve. From venomous snails to pain killers. Predator to savior. Who knew.

Lourdes Herold, Ph.D. was a professor of Chemistry at the Indiana University of Pennsylvania. She serves as the Secretary of the Philippine-American Academy of Science and Engineering (PAASE).