Shark compound proves potential as drug to treat human viruses

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A compound initially isolated from sharks shows potential as a unique broad-spectrum human antiviral agent, according to a study led by a Georgetown University Medical Center investigator and reported in the *Proceedings of the National Academy of Sciences* Early Edition online September 19.

The compound, squalamine, has been in human clinical trials for the treatment of cancer and several eye disorders, and so has a well-known safety profile, suggesting it can be quickly tested as a new class of drugs to treat infections caused by viruses ranging from dengue and yellow fever to hepatitis B, C, and D. In both lab and animal experiments, the compound effectively demonstrated antiviral activity against these human pathogens, some of which cannot now be effectively treated.

"To realize that squalamine potentially has broad antiviral properties is immensely exciting, especially since we already know so much from ongoing studies about its behavior in people," says the study's lead investigator, Michael Zasloff, M.D., Ph.D., professor of surgery and pediatrics at Georgetown University Medical Center and scientific director of the Georgetown Transplant Institute.

Not only does the study offer a promising clinical advance, Zasloff might have answered the longstanding mystery of how sharks, which have a very primitive immune system, can so effectively fight the viruses that plague all living creatures.

"I believe squalamine is one of a family of related compounds that protects sharks and some other 'primitive' ocean vertebrates, such as the sea lamprey, from viruses," he says. "Squalamine appears to protect against viruses that attack the liver and blood tissues, and other similar compounds that we know exist in the shark likely protect against respiratory viral infections, and so on.

"We may be able to harness the shark's novel immune system to turn all of these antiviral compounds into agents that protect humans against a wide variety of viruses," Zasloff says. "That would be revolutionary. While many antibacterial agents exist, doctors have few antiviral drugs to help their patients, and few of those are broadly active."

Zasloff discovered squalamine in 1993 when he was a Professor of Pediatrics and Genetics at the University of Pennsylvania searching for novel antibacterial agents. "I was interested in sharks because of their seemingly primitive but effective immune system. No one could explain why the shark was so hardy," he says.

After he began to "play" with the compound, he realized that it had other properties that offered a new direction to treat other disorders. Zasloff found squalamine inhibited the growth of rapidly growing blood vessels, such as those found in tumor growth and certain retinal diseases such as macular degeneration and diabetic retinopathy. Squalamine was subsequently tested in these conditions, and some of those clinical trials are ongoing.

Since 1995, squalamine has been synthesized in the laboratory, a process that does not involve use of any natural shark tissue.

Over the years, Zasloff remained interested in how squalamine acted as an immune agent in sharks. He knew that the compound, a natural cholesterol-like molecule, has a net positive electrical charge. He later

discovered that when it enters cells — squalamine can access only certain cells, like those in blood vessels, capillaries, and in the liver — it "kicks off" positively-charged proteins that are bound to the negatively-charged surface of the cell's inner membrane. Some of these displaced proteins are used by viruses to replicate, and Zasloff discovered that without those proteins, a virus's life cycle is disrupted, the microbe is rendered inert, and the cell that contains it is destroyed.

What most intrigued Zasloff is that squalamine seems so well designed to fight certain viral infections. "To me, the key to squalamine is that once in the body it times its action to match the life cycle of most viruses. Most viruses take hours to complete their life cycle, the same time period that squalamine renders tissues and organs viral resistant after administration. In addition, it acts fast to stop viral replication, clearing the body of these predators within hours," he says.

"Furthermore, because squalamine acts by making the host's tissues less receptive for infection, rather than by targeting a specific viral protein, the emergence of viral resistance would not be anticipated," Zasloff adds.

To help prove the potency of squalamine, Zasloff sent the compound to researchers around the country, including investigators at the University of California, Los Angeles, Utah State University, the National Polytechnic Institute of Mexico, Northwestern University, Eastern Virginia Medical School, Fox Chase Cancer Center, and the University of Texas Medical Branch at Galveston.

In tissue culture studies squalamine was shown to inhibit the infection of human blood vessel cells by the dengue virus and human liver cells infected with hepatitis B and D, which can cause liver failure and cancer.

In animal studies, his collaborators discovered that squalamine controlled

infections of yellow fever, Eastern equine encephalitis virus, and murine cytomegalovirus, and in some cases cured the animals.

"We have not yet optimized squalamine dosing in any of the animal models we have studied and as yet we do not know the maximum protective or therapeutic benefit that can be achieved in these systems," Zasloff says.

"But we are sufficiently convinced of the promise of squalamine as an antiviral agent that we intend to take this compound into humans," he says. "It is clearly a promising drug, and is unlike, in its mechanism of action and chemical structure, any other substance currently being investigated to treat viral infections."

Provided by Georgetown University Medical Center