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## Neuroinflammation, Finding A Marine Natural Product that Targets Microglia in Brain

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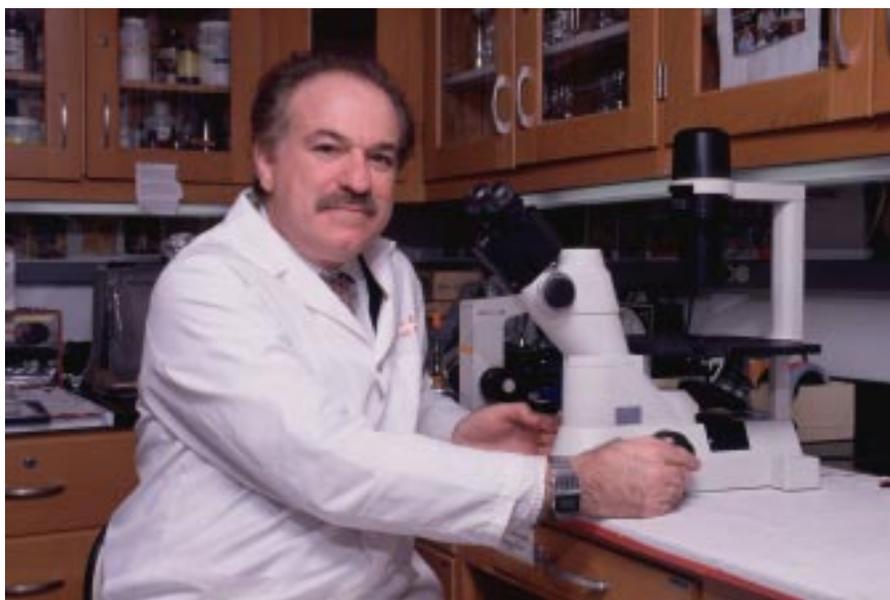
If you were to peer at brain tissue under a microscope, you would rarely see white blood cells, the body's main system of defense against infection and cancer. Their absence in the brain once led many to speculate, incorrectly, that the central nervous system must lack an immune system. In reality, it seems the brain has its own immunological sentries, a network of microglia cells that normally do not come into contact with white blood cells. This segregation of immunological duties protects the brain from neuron-damaging chemicals secreted by white blood cells.

What scientists have found out, however, is that secretions from microglia cells can also damage neurons. Normally, microglia cells have a benevolent effect. In their resting state, they vigilantly monitor the health of the neurons around them. In the event of infection or trauma, microglia cells become activated, changing shape, mobilizing and migrating to an injured area. In their battle against interlopers, they may secrete chemicals called mediators.

For reasons that are not fully understood, overzealous microglia cells sometimes deluge neurons with mediator compounds. As a result, they damage the neurons they are supposed to be protecting. It is currently believed that mediator compounds may exacerbate or help cause Alzheimer's disease, stroke and multiple sclerosis.

### The Project

The purpose of this project is to investigate whether compounds extracted from marine organisms—soft corals, sponges, tunicates,

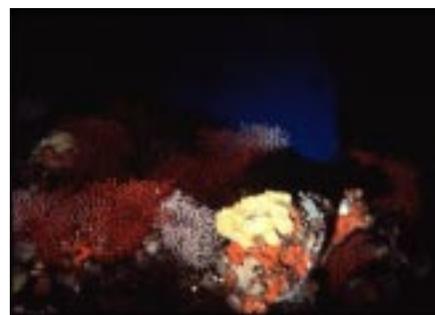


With Sea Grant funding, Dr. Alejandro Mayer studied a marine natural product that may help treat head injuries, multiple sclerosis and Alzheimer's disease. Photo: Midwestern University.

algae and bacteria—suppress, inhibit or control the release of neurotoxic mediator compounds in the brain.

Dr. Alejandro Mayer, a pharmacologist at Midwestern University in Downers Grove, Illinois was funded to conduct a pharmacological investigation of 38 compounds purified from marine organisms. Many of these pure compounds were provided by marine chemists, including Sea Grant researchers Drs. Robert Jacobs of UC Santa Barbara, and William Fenical of UC San Diego.

Of the 38 compounds tested, three showed promise in drug discovery. These three all inhibited the release of a mediator known as thromboxane B2, a cause of neuroinflammation, and superoxide, a free-radical type of mediator that may help cause Alzheimer's disease.



The yellow sponge (*Haliciona sp.*) is the source of anti-inflammatory Manzamines. Photo: Tatsuo Higa, University of the Ryukyus, Okinawa, Japan.

Dr. Mayer's most exciting finding, however, was the discovery that the marine chemical Manzamine A, extracted from a marine sponge, inhibits mediator formation in microglia isolated from newborn rats without killing healthy cells.

Mayer has since patented the

anti-inflammatory uses of  
Manzamines.

### Applications

Aspirin is an example of a nonsteroidal anti-inflammatory agent that relieves headaches by inhibiting the release of a certain type of lipid mediator in the brain. The hope is that Manzamines will lead to the development of a new class of nonsteroidal anti-inflammatory drugs that specifically target mediator production by microglia cells.

### Cooperating Organizations

Abbott Laboratories  
Harbor Branch Oceanographic  
Institution  
SmithKline Beecham  
Pharmaceuticals  
University of California  
University of Guam  
University of Mississippi

### Trainee and Thesis

Wang, Jim. Ph.D. in chemistry, University of Illinois, Urbana, "Profiling Eicosanoids by Electrospray Mass Spectrometry," June 1998.

### Patent

Mayer, A.M.S. et al. Anti-inflammatory uses of Manzamines. U.S. Patent No. 09/535291. March 24, 2000

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