

# Researchers find cancer-inhibiting compound under the sea

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University of Florida College of Pharmacy researchers have discovered a marine compound off the coast of Key Largo that inhibits cancer cell growth in laboratory tests, a finding they hope will fuel the development of new drugs to better battle the disease.

The UF-patented compound, largazole, is derived from cyanobacteria that grow on coral reefs. Researchers, who described results from early studies today (Aug. 7) at an international natural products scientific meeting in Athens, Greece, say it is one of the most promising they've found since the college's marine natural products laboratory was established three years ago.

An initial set of papers in the *Journal of the American Chemical Society* also has garnered the attention of other scientists, and the lab is racing to complete additional research. The molecule's natural chemical structure and ability to inhibit cancer cell growth were first described in the journal in February and the laboratory synthesis and description of the molecular basis for its anticancer activity appeared July 2.

"It's exciting because we've found a compound in nature that may one day surpass a currently marketed drug or could become the structural template for rationally designed drugs with improved selectivity," said Hendrik Luesch, Ph.D., an assistant professor in UF's department of medicinal chemistry and the study's principal investigator.

Largazole, discovered and named by Luesch for its Florida location and

structural features, seeks out a family of enzymes called histone deacetylase, or HDAC. Overactivity of certain HDACs has been associated with several cancers such as prostate and colon tumors, and inhibiting HDACs can activate tumor-suppressor genes that have been silenced in these cancers.

Although scientists have been probing the depths of the ocean for marine products since the early 1960s, many pharmaceutical companies lost interest before researchers could deliver useful compounds because natural products were considered too costly and time-consuming to research and develop.

Many common medications, from pain relievers to cholesterol-reducing statins, stem from natural products that grow on the earth, but there is literally an ocean of compounds yet to be discovered in our seas. Only 14 marine natural products developed are in clinical trials today, Luesch said, and one drug recently approved in Europe is the first-ever marine-derived anticancer agent.

"Marine study is in its infancy," said William Fenical, Ph.D., a distinguished professor of oceanography and pharmaceutical sciences at the University of California, San Diego. "The ocean is a genetically distinct environment and the single, most diverse source of new molecules to be discovered."

The history of pharmacy traces its roots back thousands of years to plants growing on Earth's continents, used by ancient civilizations for medicinal purposes, Fenical added. Yet only in the past 30 years have scientists begun to explore the organisms in Earth's oceans, he said. Fewer than 30 labs exist worldwide and research dollars have only become available in the past 15 years.

HDACs are already targeted by a drug approved for cutaneous T-cell

lymphoma manufactured by the global pharmaceutical company Merck & Co. Inc. However, UF's compound does not inhibit all HDACs equally, meaning a largazole-based drug might result in improved therapies and fewer side effects, Luesch said.

Since 2006, Luesch and his team of researchers have screened cyanobacteria provided by collaborator Valerie Paul, Ph.D., head scientist at the Smithsonian Marine Station in Fort Pierce. They check the samples for toxic activity against cancer cells and last year encountered one exceptionally potent extract — the one that ultimately yielded largazole.

To conduct further biological testing on the compound, Luesch and his team have been collaborating with Jiyong Hong, an assistant professor in the department of chemistry at Duke University, to replicate its natural structure and its actions in the laboratory.

Luesch said that within the next few months he plans to study whether largazole reduces or prevents tumor growth in mice.

Luesch has several other antitumor natural products from Atlantic and Pacific cyanobacteria in the pipeline.

"We have only scratched the surface of the chemical diversity in the ocean," Luesch said. "The opportunities for marine drug discovery are spectacular."

Source: University of Florida

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