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MARINE NATURAL PRODUCTS MAY PROVIDE NEW WEAPONS AGAINST CANCER AND OTHER DISEASES

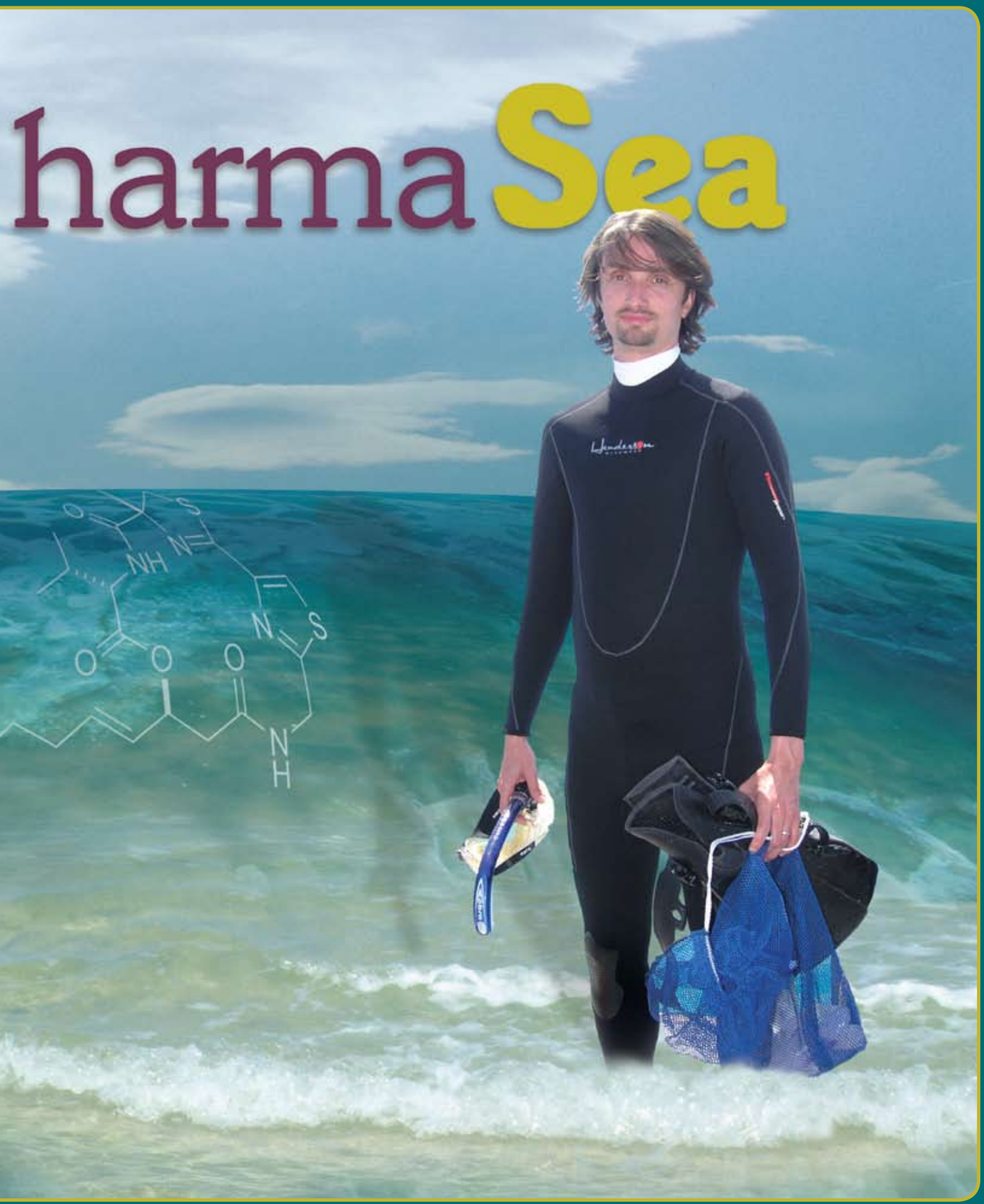
By Joseph Kays

Cyanobacteria have many names and most are not very flattering — like sea scum and red slime. Hendrik Luesch would like to improve their image by adding another name — cancer treatment.

Luesch, an assistant professor of medicinal chemistry in the UF College of Pharmacy and director of the Marine Natural Products Laboratory, collects cyanobacteria from coral reefs around the globe to study the unique toxins they produce.

Also called blue-green algae because of their resemblance to seaweed, filamentous cyanobacteria are visible to the human eye, so Luesch and his team can easily spot it growing on hard surfaces like coral, usually in shallow water.

harma Sea



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While snorkeling around some of the most beautiful coral reefs on the planet might sound like a pretty cushy way to earn a living, Luesch is quick to point out that it's not as easy as it looks.

"It's tougher than it sounds," Luesch says. "It's a lot of fun, but it's also hard work. My students can attest to that. And then the really hard work begins, in the laboratory."

The team of doctoral students and post-doctoral researchers carefully removes the cyanobacteria from the coral, stores it in plastic bags and puts it on ice. Back in the laboratory, the researchers freeze-dry the samples, then use solvents to tease out a mixture of different compounds.

"This crude extract may contain hundreds of different compounds," Luesch says. "We apply the crude extract to a variety of cancer cells to see whether it inhibits their growth. If we see any reaction, then the next challenge is to figure out which compound is causing the reaction."

By gradually refining the crude extract, "we ultimately end up with the pure compound that is responsible for the activity," Luesch says.

In 2008, Luesch identified a compound from some cyanobacteria collected in the Florida Keys that seemed to impede breast cancer cell growth better than the anti-tumor drug Taxol, without causing Taxol-like side effects on normal tissue.

Luesch named the compound largazole because it came from cyanobacteria collected off of Key Largo and because it is structurally part of the thiazole family of compounds.

But Luesch's group was able to isolate only a milligram of the compound, so he turned to Duke University chemist Jiyong Hong to try to synthesize enough of the compound to conduct mechanistic and animal studies.

"We needed to develop a concise and efficient synthetic route to make enough largazole for animal studies," says Hong.

Together with the Duke team they devised a method to produce gram-sized quantities — about 1,000 times larger — by identifying three key building blocks in largazole's ring-shaped molecular architecture.

The scientists were then able to use commercially available chemicals to make largazole in eight steps, netting what Hong calls a "very, very efficient" 20-percent yield.

"Our next task was to pinpoint the origin of largazole's biological activity," Luesch says. The molecule appeared to initiate some signaling cascades that could affect inappropriately proliferating cells but normal ones to a much lesser extent.

In the process of sleuthing this question, Luesch's group accidentally discovered that largazole was structurally similar to another molecule known to inhibit histone deacetylases or HDACs, enzymes regulating gene expression that can foment cancerous cell growth.

"Anything that inhibits HDAC activity is of great interest to academia and the pharmaceutical industry," Luesch says, "because overactivity of this enzyme class has been associated with cancer and a variety of other diseases."

With sufficient quantities of largazole in hand, Luesch was able to prove his hypothesis that largazole inhibited HDACs. Another HDAC suppressor had already been approved for the treatment of cutaneous T-cell lymphoma at the time of

UF medicinal chemist Hendrik Luesch and collaborator Valerie Paul of the Smithsonian Marine Station collect cyanobacteria in the Florida Keys.

largazole discovery, Luesch says, while just at the end of last year, the second HDAC inhibitor was FDA approved for the same disease. Others are undergoing clinical trials as anti-cancer drugs. Luesch's and Hong's groups collaborate now on follow-up research aimed at changing largazole's structure to increase its effects on cell growth.

"It could be a very good drug candidate for the treatment of various cancers," he said.

Luesch says largazole is more selective about the HDACs it inhibits compared with the originally approved drug, meaning a largazole-based drug might result in improved therapies and fewer side effects.

"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," Luesch says.

Growing up in Germany, Luesch says he became interested in natural products chemistry because he was intrigued by the complex chemical structures produced by organisms in nature, especially by marine organisms.

"I always liked going to the beach growing up in Germany," Luesch says. "But I really got interested in marine research when I started graduate school in Hawaii. That's when I began to see the huge potential in marine research."

Luesch says he was drawn to cyanobacteria because he wanted to understand why such a simple organism devotes as much as 10 percent of its genome to so-called secondary metabolism, like defense mechanisms. Luesch hypothesized that since these stretches of DNA encoded the synthesis of already "bioactive" molecules they might potentially provide drug leads.

"They produce many compounds that we think serve as defense mechanisms against competitors and predators," Luesch says. "We don't know the precise biological targets for these compounds. We know it's not to kill cancer cells, but presumably if a compound is active in a marine organism, there may be a similar-looking protein in the human body."

While there were plenty of promising candidates in the waters surrounding Hawaii, Luesch says the samples his lab received from the mostly unexplored islands of Micronesia, Guam and Palau were even more exciting.

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As a doctoral student, Luesch began collaborating with researcher Valerie Paul at the University of Guam, first analyzing her samples in Hawaii, then traveling to Guam to collect his own samples.

"The diving was even more spectacular than Hawaii," Luesch says.

After earning his doctorate from the University of Hawaii and a post-doctoral fellowship at the Scripps Research Institute in California, Luesch began looking for a place to set up a lab devoted to marine natural products.

"How did I end up at Florida?" Luesch asks. "Within the continental United States it's still the place with greatest marine biodiversity, but another reason I came to UF was because of the great nuclear magnetic resonance facilities at the McKnight Brain Institute."

As largazole demonstrated, Luesch says his lab is typically only able to isolate very small samples of the compounds they are studying, "so we need excellent NMR spectrometers and highly sensitive probes, and UF has some of the best in the country."

"Two decades ago you needed several milligrams of pure compound to elucidate the structure," Luesch adds. "Now you can do it with tens of micrograms. Just being able to go down to a much lower level with much more sensitive

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Cyanobacteria overgrowing hammer coral in Belize.

instruments allows you to look at compounds you might have missed before."

Another big selling point is the strong interdisciplinary research focus at UF.

"The College of Pharmacy being in the Health Science Center integrated with the College of Medicine, the Brain Institute and the Shands Cancer Center truly allows interactions with potential collaborators and presents the opportunity to really take discoveries from earliest stage to the clinical stage," Luesch says. "The barriers are really lower here than at many other places. That is definitely one of the selling points."

And, serendipitously, Valerie Paul had also moved to Florida, to become director of the Smithsonian Marine Station in Fort Pierce.

Paul is a chemical ecologist who is interested in chemical cues that mediate species-to-species communication in marine ecosystems. She provides many cyanobacterial samples to the Luesch lab for chemical and biological investigation. Luesch, in turn, provides her with purified compounds for which his team has established chemical structures, biological activities and target proteins.

"Our outstanding and mutually beneficial collaboration has been instrumental to my lab's success, including to the discovery of largazole," Luesch says.

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.

"With the development of high-throughput screening technology, the pharmaceutical industry was able to screen hundreds of thousands of compounds a day for bioactivity, so they went for quantity over quality," Luesch says. "Isolating natural products is inherently a low-throughput process, resulting in fewer yet much better compounds since they have been validated by nature."

Many common medications, from pain relievers to cholesterol-reducing statins, stem from natural products that grow on land, 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 says, and one drug recently approved in Europe is the first-ever marine-derived anticancer agent.

But, Luesch says there is renewed interest from the pharmaceutical industry.

"They will wait to see what academic scientists can develop," he says, "then at a certain point they will jump in."

Luesch has several other compounds under review now and is hopeful that they will also prove effective against diseases like cancer.

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

Hendrik Luesch
Assistant Professor, Department of Medicinal Chemistry
(352) 273-7738
luesch@cop.ufl.edu

Graduate students Lilibeth Salvador, Jason Kwan and Rui Wang with Hendrik Luesch.