Opening nature's medicine chest through biotechnology research

Sea Grant's commitment to certain research areas can make a significant difference over time, as OSU natural products chemist William Gerwick can attest.

THE MOST INCONSEQUENTIAL things sometimes hold the most amazing promise. Take marine algae, for instance. To most people, it's just slimy stuff coating a seaside rock or fluttering in a tide pool. To William Gerwick, it's a treasure trove of biochemicals that holds promises for better crops, healthier animals, and solving some of the secrets of human disease.

Gerwick, a professor of Pharmacy at Oregon State University, has spent more than a decade investigating marine algae and their biochemical components, searching for substances which might be used in medicine, agriculture, and industry.

Unlocking the biochemical secrets of growing things is laborious work, and it takes time. Consistent support from Oregon Sea Grant has helped Gerwick do that work, from traveling the world to find new strains of algae to testing them for chemicals they produce in minute compounds—and developing ways to culture and grow the chemical-producing cells in the lab, to help protect the resource in the wild.

Gerwick has been studying algae since his undergraduate days at the University of California at Davis, and conducted his Ph.D. research on the subject in 1981 at the Scripps Institution of Oceanography. His focus: the unusual and highly bioactive natural products many algae—particularly the blue-green marine algae known as cyanobacteria—produce as part of their own biological processes.

One important finding was the discovery that marine algae metabolize various polyunsaturated fatty acids into substances remarkably similar to prostaglandins and leukotrienes—hormones which play important roles in human and other mammal immune systems.

The chemicals may help ensure the algae's own survival. As former doctoral candidate Don Nagle, who helped Gerwick collect algae, said, "This alga is growing like fine little hair out there, and nothing seems to be eating it. That gives a slight hint there's something toxic in there."

While still working to understand what role these substances play in the algae's own biology, the researchers have also focused on how such plant-based chemicals might be used to improve human and animal health.

Besides the chemicals that mimic immunohormones, Gerwick has discovered substances which act as anti-inflammatory agents; still others are powerful toxins that might be useful as pesticides. And most recently, he has begun investigating compounds that exhibit antimicrobial, antifungal, and anti-tubercular properties, raising the possibility of even more potential benefit to human and animal medicine.

Gerwick and his colleagues collect samples of algae from different ocean and coastal environments all over the world. They have found that even among the same species of algae, different populations may produce their own, unique assortments of biologically-active compounds—important evidence to support arguments in favor of protecting biodiversity. In an effort to help protect these unique populations from overharvest, Gerwick has worked with OSU chemical engineer Gregory Rorrer, another Sea Grant-supported scientist, to develop ways to grow the algae cells in a soupy culture which maximizes cell growth rates and boosts production of targeted chemical compounds. Such systems could keep pharmaceutical companies supplied with algal cell extracts for research and production without depleting natural stocks.

One particular algal compound, named 'curacin A,' has drawn intense interest from researchers and pharmaceutical companies the world over because of its potential as an anticancer drug.

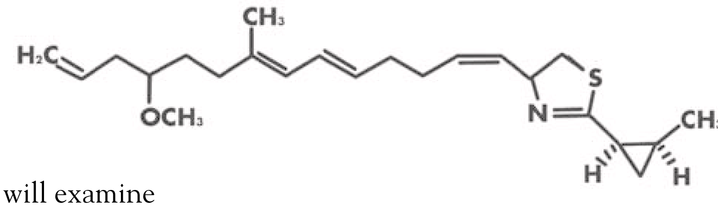
With support from Sea Grant, the National Cancer Institute, and the National Institutes of Health, among others, Gerwick has screened hundreds of new algal extracts for their anti-inflammatory, anticancer, and agrochemical activity, as well as their ability to bind with intracellular receptors (a quality important in the treatment of disease). His newest Sea Grant project will examine extracts which exhibit antimicrobial properties, opening possibilities for a whole new range of treatment for human and fish diseases caused by certain bacteria and fungi.

When a particular extract appears promising, Gerwick isolates its active compounds, analyzes their molecular structure and produces additional supplies of the material for further testing by other labs at major research institutions and pharmaceutical companies around the world.

Showing Anticancer Promise

Gerwick's work has helped identify and patent at least four new anticancer-type substances from blue-green algae:

- Curacin A inhibits cancer by binding to certain cell receptors so that the cancer cells cannot replicate themselves.
- Dolastatin 10 is undergoing National Cancer Institute-supported trials against a variety of solid tumors. Dolastatin 10 was judged to be "one of the most potent anticancer agents in vitro;" initial reports of phase I clinical testing showed that the compound "has potent activity" against small-cell lung cancer, and other research has found that the chemical has potential for treatment of leukemia and non-Hodgkins lymphoma.



One of several new algal-based compounds, Curacin A is showing promise as a possible cancer treatment.

- Cryptophycin is a by-product of algae metabolism that was first described as an antifungal compound and later shown to possess phenomenal anticancer properties. It is currently in phase II clinical trials against several common tumor types. One study, reported in *The Journal of Cancer Chemotherapy and Pharmacology*, found cryptophycin to be "significantly more potent and less sensitive to multidrug resistance mechanisms than other antimitotic antitumor agents currently used in cancer therapy."
- Tolytoxin and related scytophycins are substances which inhibit cancer cell proliferation by novel mechanisms.

The projects mentioned in this report were funded by the NOAA Office of Sea Grant and Extramural Programs, U.S. Department of Commerce, under grant number NA36RG0451, project numbers R/BT-1, R/BT-18. R/BT-09, R/BT-08, R/BT-02, and by appropriations made by the Oregon State legislature.