FEATURE STORY

Surf & Turf

BY JENNIFER M. GANGLOFF

From sea to soil, nature spurs cancer drug development.

Humans have turned to plants, animals and other products of nature for thousands of years to soothe their ills, from coughs and colds to pain and parasitic infections. Natural products fell out of favor for a time during the past couple decades because of the improved techniques to make a drug from scratch, but products from the environment are making a resurgence in research, and experts say they offer enormous potential to treat cancer and other diseases.

Natural products were considered to be an expensive and difficult way to discover new drugs, and most drug companies dropped their programs," says researcher David Sherman, PhD, the John G. Searle professor of medicinal chemistry and director of the Center for Chemical Genomics at the Life Sciences Institute at the University of Michigan. "But there's growing interest in natural products because there's been disappointment in the ability to synthetically produce compounds."

Wyeth is one of the drug manufacturers that has a dedicated program to develop natural products that dates back to the 1940s. Wyeth has historically focused research on microbial sources from the soil, mainly fungi and a form of bacteria called actinomycetes, says Guy Carter, PhD, assistant vice president for chemical sciences and screening and director of Wyeth's natural products discovery group. "There has been a resurgence in natural product development, but it's really a recognition in the industry that we'd like to have more diversity feeding into the drug discovery pipelines," Dr. Carter says.

Mylotarg (gemtuzumab), one of Wyeth's most well-known cancer drugs, was the result of a discovery by a curious scientist who spotted an interesting rock while on vacation in Texas in the late 1980s. Thinking the rock might contain useful fungi or bacteria, he toted it back to a lab in New York, grew cultures and found it contained a compound called calicheamicin (named for the caliche dirt of Texas), a potent anti-tumor antibiotic. It was chemically coupled with an antibody and became the first Food and Drug Administration-approved agent in a new class of anticancer medications called antibody-targeted chemotherapy. Wyeth still sometimes sends soil-collection kits along with vacationing staffers, Dr. Carter says. "It's been quite effective for us. Thirty years ago, that was the major way we were getting new materials to work on."

Wyeth launched a concerted effort over the past 15 years to investigate marine microbes as potential anticancer compounds. "We're finding an awful lot of life in the ocean that hasn't been fully explored," says Dr. Carter.

Resource Waiting To Be Tapped

Scientists collect specimens as broadly as they can. They collect items that have a history in folk medicine and in areas that have higher yields, like the barrier reef or rain forests. Often without solid leads, it's a process of collecting and screening. "If we go into the lab and try to make a compound from scratch, it can take three to five years. But microorganisms can make these compounds in huge quantities in minutes," says Dr. Sherman, who regularly goes on diving expeditions to collect marine life that may one day become the basis for a cancer drug.

Natural products, any small molecules derived from a living organism that occur naturally in land or sea, are obtained from a range of organisms, including microbes living on sea sponges thousands of feet under water in the South Pacific, plants in the tropical forests of Madagascar and bacteria thriving in the soil of the arctic tundra. Although some naturally occurring organisms may cause cancer—to wit, the bacterium *Helicobacter pylori* is associated with stomach cancer and human papillomavirus can cause cervical cancer—other natural products are used to treat cancer.

In fact, more than half of the anticancer drugs now on the market have their origins in nature. While some of these drugs come directly from marine or land organisms, others were synthesized, or man-made, in the lab based on Mother Nature's design. The antineoplastic antibiotics Adriamycin/Doxil (doxorubicin), Blenoxane (bleomycin) and Mutamycin (mitomycin) are all natural products produced directly by bacteria.

View Illustration: Global Findings: Nature & Drugs

Dr. Sherman and other experts in the field of natural product drug discovery say millions of years of evolution have turned plant and marine life into rich resources simply waiting to be utilized. Estimates suggest that less than 30 percent of the 250,000 known vascular plant species, which include flowering plants and ferns, have been investigated for their ability to interact with cancer cells, and a mere 1 percent of bacteria and 5 percent of fungi have even been identified. "The numbers yet to be investigated boggles the mind," says chemist David Newman, PhD, acting chief of the National Cancer Institute's Natural Products Branch, which is responsible for coordinating programs to discover and develop naturally derived products to treat cancer.

Scientists first began a serious search for anticancer compounds in nature in the 1960s, following the discovery and subsequent development of Velban (vinblastine) and Oncovin (vincristine). These drugs, which now treat a variety of cancers, are known as vinca alkaloids and are derived from the periwinkle plant, *Cat Catharanthus roseus*, sometimes called the Madagascar periwinkle, a perennial evergreen herb.

The NCI launched a formal specimen collection program in 1960, and over the

next 22 years, researchers collected and tested tens of thousands of plants, microorganisms and marine species from around the world. The NCI put each item through a variety of biological assays that tested the material's effects on living organisms and the ability to kill cancer cells. Chemists were then given the task of extracting promising specimens' active ingredients.

One of the most well-known cancer drug success stories to come out of the NCI program is Taxol (paclitaxel), a drug derived from the bark of the Pacific yew tree in Oregon and Washington, first collected at random by a botanist in 1962. "There isn't a chemist alive who would have been able to make Taxol on their own," Dr. Newman says. Taxol is used to treat breast and ovarian cancer, among others.

Both Hycamtin (topotecan), used to treat ovarian and small-cell lung cancer, and Camptosar (irinotecan), for colorectal cancer, arose from the discovery in 1958 of the cancer-fighting compound camptothecin in the bark of a tree native to China. In addition, a Caribbean sea sponge discovered in the early 1950s eventually gave rise to cytosine arabinoside (ARA-C), now used for certain types of leukemia. Aside from these and a few others, the NCI's massive collection effort yielded little success, and it was discontinued in 1982. But just four years later, with the advent of better screening methods to test effectiveness against cancer cells, the NCI revived its collection program.

Today, the NCI contracts with botanical, academic and marine research organizations to collect, store and test samples. An NCI repository in Frederick, Maryland, houses more than 70,000 plant samples, 30,000 microbes and 15,000 marine invertebrates and algae collected from more than 25 tropical and subtropical countries worldwide. The real beauty of the drug development program, though, is that it forges connections between academic researchers and pharmaceutical companies—the kinds of connections needed to guide drugs from seaside to bedside.

View Chart: Natural Products in the Pipeline

Doing Nature One Better

Dr. Newman is excited about the renewed interest in natural product development. Still, he says, it's unlikely that researchers will discover another Taxol—which was essentially unaltered from its natural state before being used in people. "The 'low-hanging fruit' has probably all been harvested already," he says.

On the other hand, scientific advances allow researchers to manipulate compounds in hundreds of ways, which means a product that may not work straight from nature can be tweaked to find something useable—and perhaps even better. That was the case with a drug currently known simply as E7389, a synthetic version of halichondrin B, which is a naturally occurring substance found in sea sponges that live in the South Pacific. Japanese researchers discovered the compound in 1986 and saw that it had very potent anticancer activity. But the natural supply was exceedingly small. "We got 300 milligrams of pure compound from one metric ton of sponge," Dr. Newman notes. Over the next decade, scientists at the Japanese pharmaceutical company Eisai worked on

synthetic versions—more than 200, in fact. In collaboration with the NCI, they ultimately came up with E7389, which proved to be an even more effective anticancer compound than the natural product. E7389 is now in clinical trials for advanced, refractory breast cancer and hormone-refractory prostate cancer.

Getting products like this to market can still take years of research, with many failures along the way. Only seven anticancer drugs derived from plants have ever been approved by the FDA: Taxol, Velban, Oncovin, Hycamtin, Camptosar, VePesid (etoposide) and Vumon (teniposide). No new plant-derived drug has entered the marketplace since 1996, and no anticancer compound directly isolated from a marine source has yet been FDA approved (chemists produced ARA-C synthetically before actually pinpointing the compounds produced naturally). But researchers are energized by promising results from clinical trials testing Yondelis (trabectedin, also known as ET-743), a compound derived from a sea squirt that is being studied in sarcoma and other solid tumors (see chart). In addition, a number of additional nature-derived anticancer drugs are in active clinical development, including a class of drugs called epothilones made from soil bacteria.

Hope and Challenge

The very thing that makes natural products so attractive can also make them difficult to work with. That's because many organisms have developed such potent chemical weaponry that they're just too toxic for human use. In addition, researchers often have little to go on when they collect samples, so they don't know in advance whether a substance will have anticancer properties or unacceptable side effects—and they may not find out until human testing.

Despite all of the promise, researchers face several obstacles in their quest to find drugs from natural products, particularly from sea life. Beneath the ocean a quiet battle rages even among the simplest of animal life forms, including coral, sea sponges and sea squirts, as they compete for suitable food and territory and fend off predators. Because of this competition, many marine species, particularly those that are immobile, have developed highly toxic chemicals as a means of defense—chemicals that may be able to kill cancer cells because of their interactions with cell receptors and enzymes.

But collection is a major obstacle. Divers like Dr. Sherman can gather samples when the specimens aren't too deep. Deep-water collection may require the use of unmanned submersibles, which can be cost-prohibitive at thousands of dollars a day. Dredging and trawling have been used, but pose their own problems, including difficulty accessing niche areas and destruction of the ecosystem.

David Sherman, PhD, and his team collected more than 1,500 samples during a diving expedition to Papua New Guinea in 2005. Photo by Zachary Beck, PhD/Life Sciences Institute.

Supply is another common challenge. For instance, to make 18 grams of the natural product bryostatin 1 for use in clinical trials, researchers had to collect

some 28,000 pounds of *Bugula neritina*, a moss-like marine invertebrate known as a bryozoan. Scientists are trying to create sustainable supplies of marine organisms by growing them in underwater farms, in silo-like fermentation tanks on land and simply in flasks that sit on lab shelves. They're also trying to clone the blueprint DNA that specifies production of natural products derived from microbial sources in order to make synthetic or semi-synthetic versions that mimic the natural organisms.

Learning more about the complex relationships between marine microorganisms and marine invertebrates may also help. It was only recently that scientists realized many of the cancer-fighting compounds they sought from marine organisms, like the sponge, actually may come from microscopic bacteria that live symbiotically with it. "The field is only in its infancy," Dr. Sherman says. "There are still huge challenges, but there is also definite success."