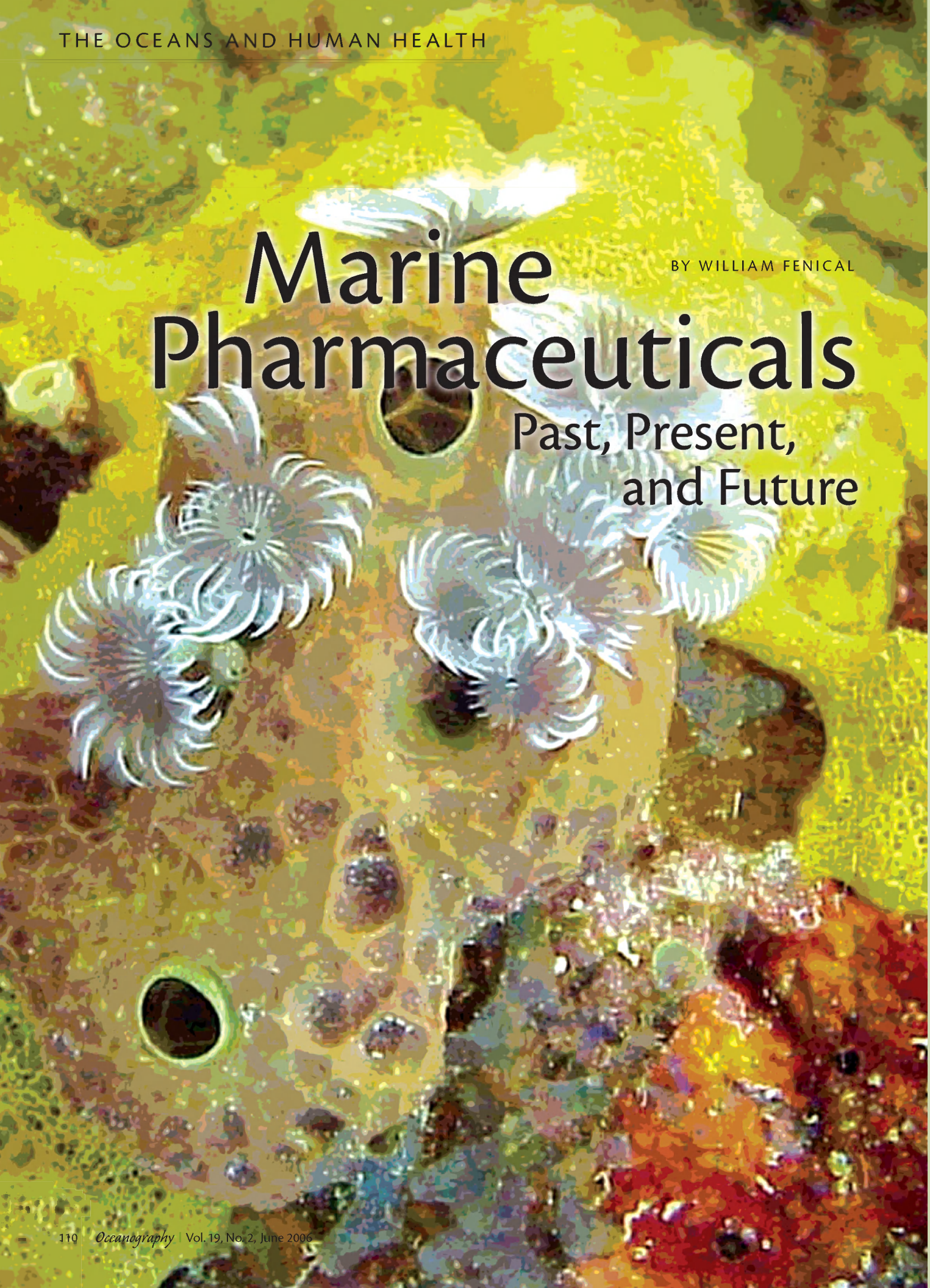
Marine Pharmaceuticals

Past, Present, and Future

BY WILLIAM FENICAL



BENEFICIAL ROLE OF THE OCEANS?

In this issue of *Oceanography*, the majority of the papers presented focus on the harmful health effects of the oceans created by oceanic events, anthropogenic influences, and harmful marine life. These are important issues that dramatically affect human health, but at the same time this view does not reflect the fact that we are just now realizing some of the health-related benefits from the oceans. Comprising 34 of the 36 Phyla of life, marine ecosystems are indeed our last genetic diversity and biotechnological frontier; terrestrial systems possess only 17 Phyla. We have much to learn.

Humankind has explored and exploited the terrestrial environment for more than 3000 years, leading to the examination of almost every possible resource on land. In the future, similar explorations of the world's oceans, using modern chemical and molecular genetic technologies, will uncover a rich treasure chest of new medicinal products, cosmetics, foods, industrial chemicals, and new, environment-friendly industrial processes. As we have benefited from life on land, it is reasonable to predict that the next few decades will be filled with new discoveries from our greatest untapped resource, the world's oceans. In this short synopsis, I will attempt, admittedly in a non-comprehensive way, to summarize the past and current status of marine medicine, and to emphasize the important role the oceans will play in human medicine in the decades to come.

NATURAL PRODUCTS AND THE TREATMENT OF HUMAN DISEASE

More than 3000 years ago, early societies recognized that the diversity of plant life around them could be used for the treatment of human illness. Natural "preparations," in the form of teas or salves derived from plants, were commonly used to treat pain, infections, gastrointestinal maladies, inflammation, cancer, and many other common illnesses. Traditional healers evolved who were consulted to treat illness, and the knowledge of these individuals was passed down to understudies or apprentices who continue to practice today. Today, for economic as well as traditional reasons, much of the developing world still relies on natural medicines (e.g., ethnomedicines or traditional medicines) for the treatment of human disease.

Over time, the "active ingredients" from traditional medicines were chemically purified, and during the 19th and 20th centuries some of these drugs (e.g., morphine, quinine, the salicylates [aspirin]) were utilized in single-ingredient formulations (i.e., "drugs"). As time passed, these molecules became the foundation of the new discipline of organic chemistry. The developing pharmaceutical industries evolved to focus their efforts on purifying new drugs from these traditional ethnomedicines (Therapeutic Research Faculty, 2006).

The discovery of penicillin in the late 1920s by Alexander Fleming was perhaps the single most important medical discovery in modern times. This, and subsequent discoveries by Selman Waksman (i.e., actinomycin and other antibiotics) and other researchers, changed how drugs were discovered and how Nature was explored (Bérdy, 2005). The pharmaceutical industry, worldwide, quickly evolved by embracing these findings, and subsequently discovered hundreds of "wonder drugs" that had the capability to cure pneumonia and almost all bacterial infectious diseases. These natural "wonder drugs" saved millions of lives during and after World War II, and gave us the false sense that the great plagues of the past (e.g., cholera) would never again be seen (see Laws case study, this issue). More than 120 antibiotics, anticancer agents, and other therapeutics originally derived from microorganisms that are found in soil are still prescribed today.

DISCOVERY OF THE OCEANS IN THE 1960s—THE PAST

It is interesting to note that, historically, the oceans were rarely considered as a likely source for natural medicines. In southern China, a poorly described marine ethnomedicine evolved, but this approach was not generally seen elsewhere. Despite biologists exploring life in the oceans in the 18th and 19th centuries, the linkage of medicine and marine biodiversity was never made. Even in more modern times, the pharmaceutical industries made little effort to examine life in the sea. This is understandable because the ocean was virtually unknown, and difficult and dangerous to explore, while new drugs from terrestrial plants, and later soil microorganisms, were plentiful.

As a consequence, the enormous resources of the oceans lay dormant until the mid to late 1960s when small groups of organic chemists in the United States, Europe, and Japan began to collect, extract, and chemically explore the diversity of marine life. Pioneers like Paul Scheuer and Richard Moore in the United States, Luigi Minale and Ernesto Fattorusso in Italy, and a small group of Japanese researchers (who were already the

leaders in marine toxin research), began to examine sponges, marine algae, and other unfamiliar forms of marine life. To their great surprise, new molecules of unprecedented types were found (Faulkner, 2000a, 2000b). The structures of entirely new chemical entities, which challenged accepted biosynthetic understanding, were published at an impressive rate. These pioneering chemical researchers, who were amateur biologists at best, found that marine animals possessed a rich new chemistry that had never been seen before. It then became clear that the oceans were indeed a new and exciting resource (Figure 1).

THE "EXPLORATORY DECADE"

During the 1970s, small groups of chemists continued to explore the amazing diversity of novel molecules present in marine organisms. Their goal was to fully comprehend the sources of these molecules and the extent to which these new compounds were different from those produced by terrestrial plants and microorganisms. Chemical structures were found that completely changed the foundations of natural-product biosynthesis. Perhaps to be expected, the halogens (i.e., iodine, bromine, and chlorine, but not fluorine) were found to play prominent roles, not only as substituents in complex molecules, but also by acting as reactants (in halocyclization reactions, for example) to create entirely new classes of terpenoids and other structure classes of bioactive molecules (Figure 2). In a mere ten-year span, the complexity of terpenoid biosynthesis was more than doubled! Molecules possessing unprecedented functional groups such as carbonimidic dichlorides (Wratten and Faulkner, 1977) and molecules of unprecedented size and complexity, such as the polyether toxin brevetoxin-B (Lin et al., 1981), were isolated and identified. The new field of marine natural products chemistry had been initiated with a resounding success.

In the beginning, financial support to expand this entirely new and exploratory science was very difficult to obtain. Ocean scientists asked why this was being done? But the chemists, who were largely not trained as marine scientists,

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Figure 1. Close-up underwater photograph of the invertebrate and plant diversity typically observed on coral reefs. Diversity can reach 1000 species per square meter.

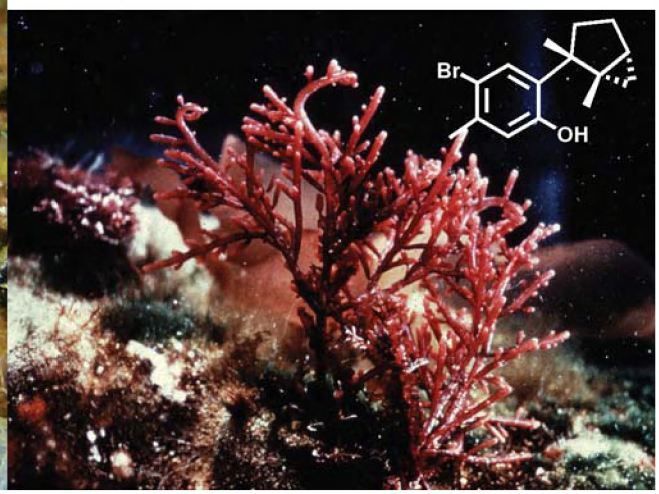


Figure 2. The widely distributed red seaweed *Laurencia* was the first to be recognized as a robust source for halogenated natural products. This and related seaweeds produce a diversity of halogenated compounds (some with 5–6 bromine and chlorine atoms) by processes involving halogenating enzymes. Laurinterol (shown) was the first brominated terpene to be isolated (1968).

knew that they had uncovered an amazingly complex new science, one that would ultimately explain much of the ecology of marine life. In the funding arena, the National Sea Grant Program (United States) was a clear exception. The founders of this program, who had the wisdom to envision the discovery of marine drugs, were rewarded by the huge successes that were subsequently achieved. Later, the Divisions of Chemistry and Ocean Sciences at the U.S. National Science Foundation became involved, showing an interest in this new and developing field of study. No one knew where this was going, but everyone saw the potential for the future. Beginning in the early 1980s, a new component of marine ecology, "marine chemical ecology," was established by a small group of scientists who used this chemical knowledge base to demonstrate that bioactive molecules produced by (mainly) soft-bodied marine plants and animals are the foundation of an elaborate strategy of chemical defense and communication in the ocean (Hay, 1996, 2002).

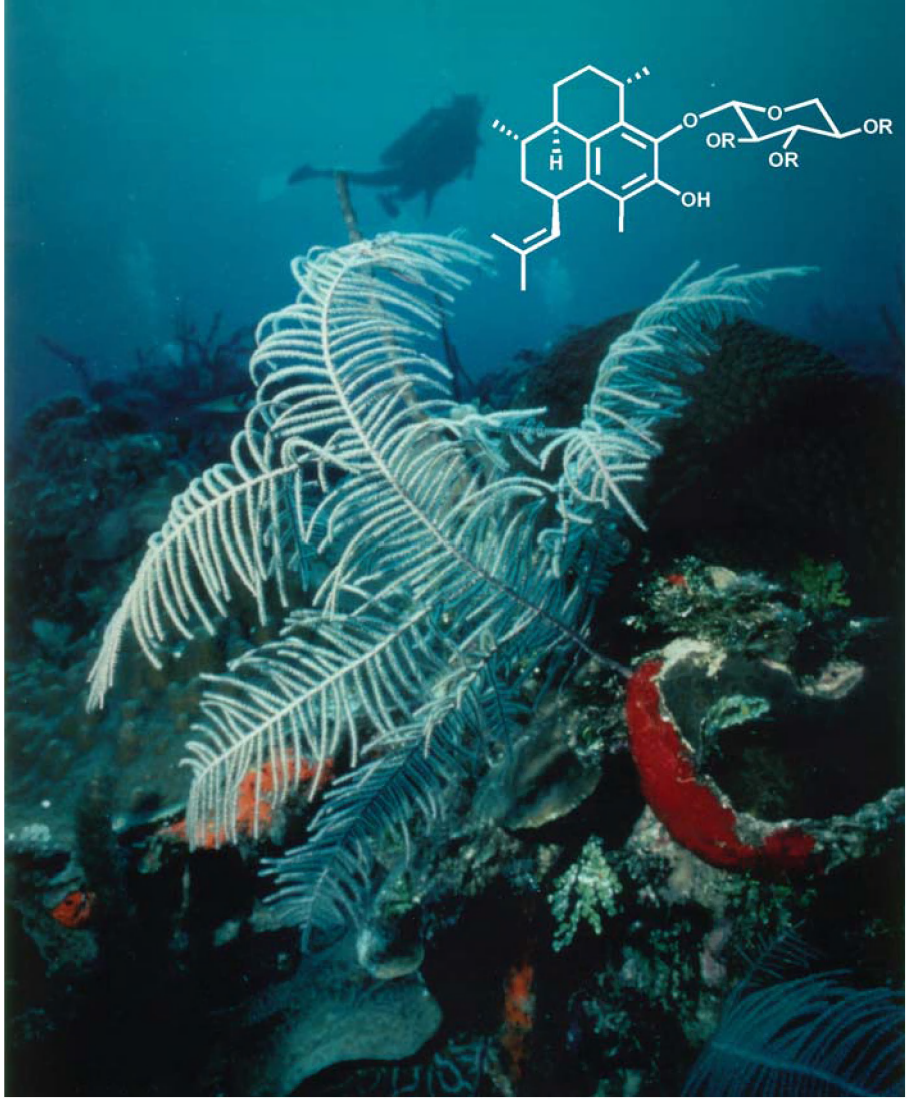


Figure 3. The Caribbean sea whip, *Pseudopterogorgia elisabethae* (Gorgonaceae), contains the pseudopterosins (shown) which possess potent topical anti-allergenic and anti-inflammatory properties. Estee Lauder, in collaboration with California Sea Grant researchers, developed these agents as skin care additives. The first application was in their "Resilience" cosmetic line. Photo courtesy V.J. Paul, Smithsonian Institution Marine Laboratory, Fort Pierce, Florida.

COULD THESE MOLECULES BE DRUGS? CONNECTIONS WITH INDUSTRY AND PHARMACOLOGY

On the basis of the recognized "promise of the sea," many researchers in the mid to late 1980s began to see how the complex chemistry from the marine environment could be applied to improving human health. Academic researchers probed industry, seeking collaborations, and approached the National Institutes of Health (NIH) to support these developing studies. Although slow, successes continued to be seen.

With the help of Estee Lauder scientists, Sea Grant researchers in California developed a new skin-care additive "pseudopterosins" from the Caribbean sea whip *Pseudopterogorgia elisabethae* (Figure 3) (Look et al., 1986). This product, still in use today, dramatically reduces the allergenic responses of skin lotions to some individuals and provides strong anti-inflammatory properties. This product was perhaps the first clinically validated "cosmeceutical" derived from a marine source. During this same period, both the National Cancer Institute (NCI) and many researchers began to see the promise of the marine environment in the treatment of cancer. The NCI had undertaken a screening program ten years earlier, and they were finding that marine samples provided the highest potential for anticancer drug discovery. Evidence that this would ultimately be a successful endeavor came from the subsequent isolation of a broad structural diversity of more than 500 molecules

that had the ability to inhibit the growth of cancer cells at sub-micromolar concentrations. These highly bioactive molecules came mainly from sponges, ascidians, and bryozoans, classes of marine invertebrates that are now recognized as the most chemically prolific of all the marine animal groups (Figure 4).

DISCOVERIES AND SUCCESSES—CURRENT

Many natural products were developed into medicines in the mid 20th century, but the challenges and difficulties to do so now have dramatically changed. In the 21st century, we live in a more complex world in which diseases are complex and resistant to cures. With the past in mind, society now places exceptionally strong demands on drug safety and efficacy. As a consequence, many of the drugs developed in past years would not survive today's high-level expectations. Drug resistance in the treatment of cancer and infectious diseases is emerging at a frightening rate, just when the pharmaceutical industries are turning away from some of these areas, only to focus their attention on the development of "block-buster drugs" (sales in excess of $2 billion) in therapeutic areas requiring chronic treatment over a lifetime. Explorations for new anti-infective agents, especially antibacterial drugs, have all but ceased. Given these new realities, how can the biomedical potential of the oceans best serve human medicine?

Over the past ten years, the oceans have provided exciting medical discoveries that are now yielding drugs. The first marine drug was Ziconotide (Pralt™), a potent pain medication that was developed based upon knowledge of the highly toxic small peptide ω-conotoxin MVIIA extracted from the venomous gastropod mollusk *Conus magus* (Figure 5) (Olivera et al., 1987). Ziconotide, a potent calcium channel blocker, is the only drug in this class of agents that provides relief from severe neurogenic pain. Although this is the first marine drug generally recognized, in the 1950s, Werner Bergman, a pioneer in marine sterol chemistry, isolated two

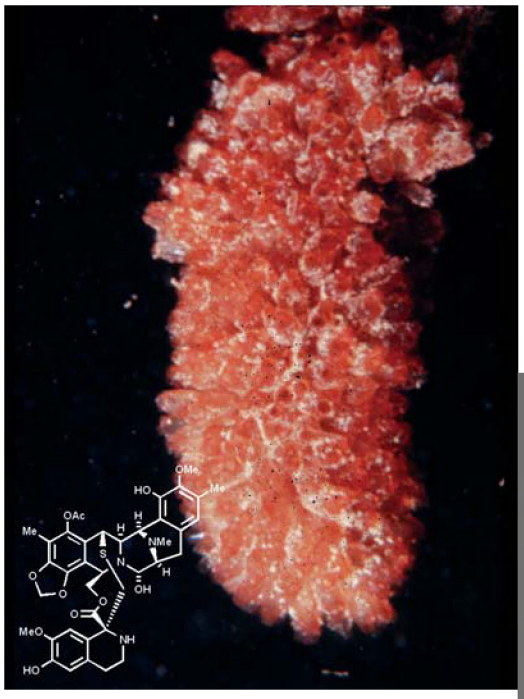
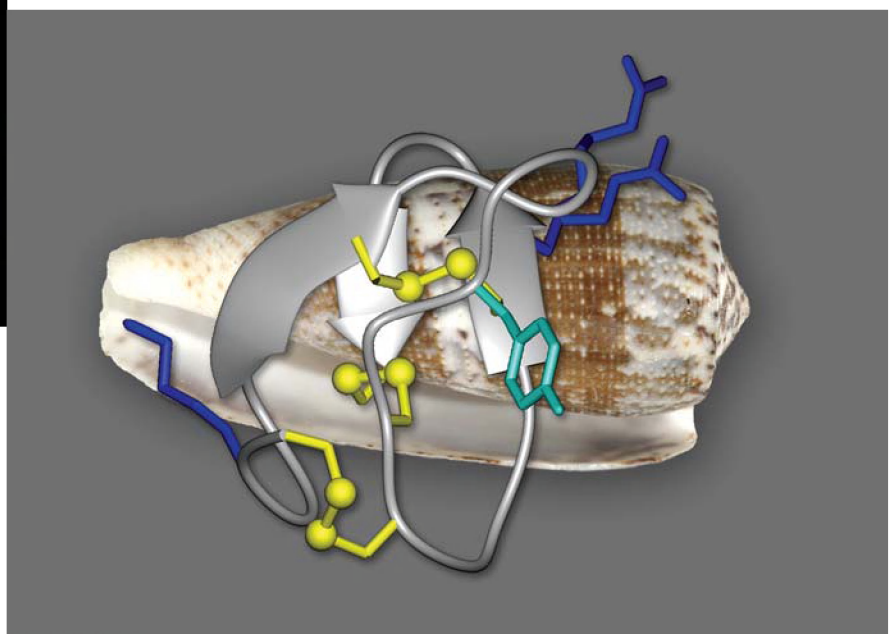


Figure 4. An underwater photo of the ascidian, *Ecteinascidia turbinata*, growing on hanging mangrove prop roots. This animal contains ecteinascidin 743 (shown), a powerful anticancer agent currently in advanced clinical trials.

Figure 5. The cone snail, *Conus magus*, produces the potent analgesic peptide ω-conotoxin MVIIA (or ziconotide, shown). A synthetic version of this peptide is currently marketed for intense neurogenic pain under the trade name Prialt™. Mollusks of the genus Conus produce numerous highly bioactive peptides that are in clinical trials for pain relief and treatment of asthma and Alzheimer's Disease. Photo courtesy B. Olivera, University of Utah, Salt Lake City, Utah.



modified nucleosides, spongothymidine and spongouridine, from the sponge *Cryptotethia crypta* (Bergman and Feeney, 1951). These compounds possessed unique antiviral activities, and over the decades were the inspiration for the development to two related antiviral drugs, Ara-A (Vidabarine) and Ara-C.

As might be expected, the large pharmaceutical industries have had only modest interest in embracing marine-drug discovery. This area continues today to be one of uncertainty and high predicted risk, and one that industry has not learned to reliably control. As a consequence, more and more discoveries are being made by academic researchers and by the flourishing small biotechnology industries (see Toledo et al. case study, this issue). Increasingly, the large pharmaceutical industries rely on the "in-licensing" of drugs discovered elsewhere (Table 1). Thus, in the decades to come, it can be predicted that marine biotechnology companies will evolve as opportunities arise to exploit marine biodiversity.

Cancer continues to be a major disease worldwide; in the United States, Europe, and Japan it is a major cause of human mortality. It is thus no surprise that the NCI has invested heavily over the past three decades in the discovery and development of anticancer drugs from marine sources (Cragg et al., 2005). What is not widely known is the degree of their success. In 2006, more than 30 marine-derived molecules are in preclinical development or clinical trials against a wide diversity of cancers. A significant number of these new drug candidates was developed with direct or indirect NCI assistance, and once brought to the point of perceived utility, they were then licensed to pharmaceutical partners for clinical development, manufacture, and sales.

Of particular importance over the past 15 years is the NCI's "National Cooperative Drug Discovery Groups" or NCDDGs, and productive researchers such as G.R. Pettit at Arizona State University's Cancer Research Institute, who have dedicated their work to cancer-drug discovery (Figure 6). The NCDDG collaborative grants were cleverly crafted to require the close collaboration of academic researchers and industrial scientists, whose respective abilities to focus on new sources for possible drugs were coupled with the pharmacological strengths and developmental expertise of industry. The result has been productive collaborative programs that link these diverse scientific endeavors (Figure 7). Table 1 lists the cancer drugs discovered in these and related programs, their sources, and discoverers. Seventeen novel molecules, produced by marine bacteria, sponges, ascidians, mollusks, bryozoans, and sharks, are currently in clinical trials. This impressive list can leave no doubt that the oceans have the ability to offer new pharmaceuticals, particularly for the treatment of cancer.

It is often asked why marine sources should yield new anticancer agents? Is it simply that the oceans contain many potent toxins, and these are useful in killing cancer cells but have no other utility? This is an inaccurate view of the medical potential of the world's oceans created by the significant funding available worldwide to discover new anticancer drugs. Marine life produces a massive diversity of complex, bioactive molecules only a small percentage of which is "toxic" to humans and other species in the traditional sense. These molecules are now being shown by academic researchers to possess diverse and highly complex pharmacological properties with applications to many diseases. Many unique molecular probes with activities relevant to fundamental processes have been isolated and defined. The problem of developing a greater diversity of marine drugs lies in the lack of funding for the discovery of drug leads in other therapeutic areas. As of 2006, the NCI is the only NIH institute that had a dedicated drug-discovery program (Cragg et al., 2005). Furthermore, there is an undeveloped relationship between those who discover new marine molecules and those who have the biological expertise and screening capacity to develop new drugs in diverse therapeutic areas. Impressively, three new marine drugs are in clinical trials for acute pain, three more are in clinical evaluation for the treatment of asthma, and one drug is in clinical assessment for Alzheimer's Disease (Table 1). Other molecules are being shown to be effective against malaria and other infectious diseases. Indeed, today, the study of bioactive marine molecules continues at a spectacular pace (Blunt et al., 2003, 2004, 2005).

While the ocean is clearly a new frontier in drug discovery, it remains isolated from the mainstream discovery and developmental processes, which require hundreds of millions of dollars of investment. How can we change this? One can predict that the next decade will see major changes in the pharmaceutical industry and in how NIH will respond to medical discoveries and human medical needs. More academia-industry linkages will be observed, and the responsibility

Table 1. Status of Marine-Derived Natural Products in Clinical and Preclinical Trials

Compound Name	Source	Status (Disease)	Comment
Bryostatin 1	Bryozoan *Bugula neritina*	Phase II (Cancer)	Now in combination therapy trials; licensed to GPC Biotech by Arizona State University
TZT –1027	Synthetic Dolastatin	Phase II (Cancer)	Also known as Auristatin PE and Soblidotin
Cematodin	Synthetic derivative of Dolastatin 15	Phase I /II (Cancer)	Some positive effects in melanoma
ILX 651, Synthatodin	Synthetic derivative of Dolastatin 15	Phase I/II (Cancer)	For melanoma, breast, and non-small cell lung cancer (NSCLC)
Ecteinascidin 743	Ascidian *Ecteinascidia turbinata*	Phase II/III (Cancer) in 2003-2005	Licensed to Ortho Biotech (J&J/Janssen Pharmaceuticals)
Aplidine	Ascidian *Aplidium albicans*	Phase II (Cancer)	Dehydrodidemnin B; made by total synthesis
E7389	Sponge *Lissodendoryx sp.*	Phase II (Cancer)	Eisai's synthetic halichondrin B derivative; breast and lung
Discodermolide	Sponge *Discodermia dissoluta*	Phase I (Cancer)	Licensed to Novartis by Harbor Branch Oceanographic Institution
Kahalalide F	Mollusk *Eylsia rufescens* and Alga *Bryopsis sp.*	Phase II (Cancer)	Licensed to PharmaMar by University of Hawaii
Zalypsis	Synthetic Safracin B derivative	Phase I (Cancer)	PharmaMar (based on saframycin molecule)
ES-285	*Spisula polynyma*	Phase I (Cancer)	Rho-GTP inhibitor
KRN-7000	Sponge *Agelas mauritianus*	Phase I (Cancer)	An agelasphin derivative
Squalamine	Shark *Squalus acanthias*	Phase II (Cancer)	Anti-angiogenic activity as well
Æ-941 (Neovastat)	Shark	Phase II/III (Cancer)	Defined mixture of < 500 kDa from cartilage; anti-angiogenic
NVP-LAQ824	Synthetic	Phase I (Cancer)	Derived from Psammaplin, Trichostatin and Trapoxin structures
E-7974 (Eisai)	Synthetic	Phase I (Cancer)	Carboxylate-end modified hemisasterlin
Salinosporamide A (NPI-0052)	Bacterium *Salinispora tropica*	Phase I (Cancer)	Proteasome inhibitor Nereus Pharma
GTS-21 (aka DMBX)	Marine worm	Phase I (Alzheimer's)	Licensed to Taiho by the University of Florida
IPL-576,092 (aka HMR-4011A)	Sponge *Petrosia contignata*	Phase II (anti-asthmatic)	Derivative of contignasterol; Inflazyme Pharma
IPL-512,602	Derivative of 576092	Phase II (anti-asthmatic)	With Aventis. No further data as of 08/2005
IPL-550,260	Derivative of 576092	Phase I (anti-asthmatic)	With Aventis. No further data as 08/2005
Ziconotide (aka Prialt)	Mollusk *Conus magus*	Approved FDA 28DEC04 (Neuropathic pain)	Licensed by Elan to Warner Lambert; launched in U.S. and Europe in 2005
CGX-1160	*Conus geographus*	Phase I (Pain)	Cognetix and Elan Corporation (Ireland); Phase II late 2005
ACV1	*Conus victoriae*	Phase I (Pain)	Metabolic Pharma (Australia)(06/2006), conotoxin Vc1.1

This table was adapted from information kindly provided by David J. Newman, National Cancer Institute, Bethesda, MD, USA.

for drug discovery, particularly in the less-profitable areas such as antibiotics discovery, will be more greatly embraced by the NIH. These changes are beginning now with industry reconsidering natural product-based drug discovery and the NIH planning their own drug-discovery efforts as part of the "NIH Roadmap for Medical Research" (for more information go to http://nihroadmap.nih.gov).

NEW MARINE BIOMEDICAL SCIENCES—THE FUTURE

We are about to enter an exciting new era in medicine, one that is already embracing a new paradigm involving genomics-based drug discovery. Not only will knowledge of the human genome provide new drug targets and assist in disease diagnoses, but sequencing the full genomes of marine life will illustrate entirely new biosynthetic pathways that code for the production of a diversity of compounds as yet undiscovered. Genes from new and diverse marine sources will be cloned, combined, and expressed to generate a huge diversity of new molecular architectures. New resources, which had been difficult to examine in the past, will now be the focus of significant study. A prime example is the taxonomically complex microbial life that resides in the world's oceans. In contrast to terrestrial microbes, which formed the foundation for drug discovery for more than 40 years, those adapted for life in the sea are only superficially known.

Advances in genomics-based taxonomy, and in the acquisition and cultivation of marine bacteria, are already leading to the recognition of new classes of bacteria that produce unprecedented antibiotics and potential anticancer drugs. Shotgun cloning of DNA directly

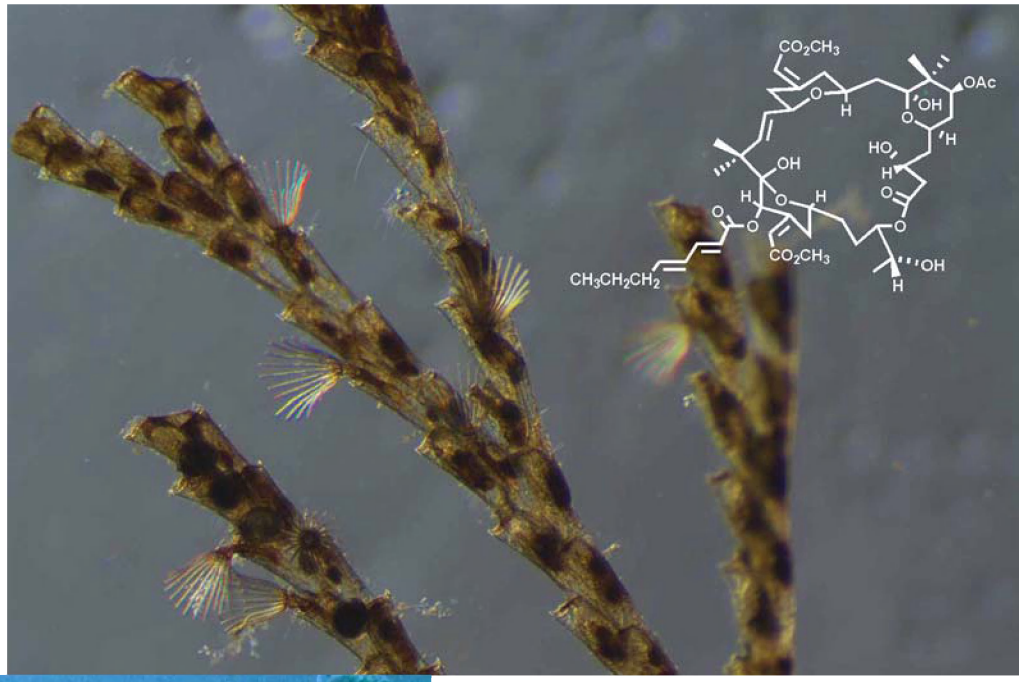


Figure 6. The bryozoan *Bugula neritina* contains complex macrolides, exemplified by bryostatin I (shown), which show unique properties in the treatment of human cancers. Bryostatin I is currently in clinical trials. Photo courtesy K. Sharp, Scripps Institution of Oceanography, La Jolla, California.

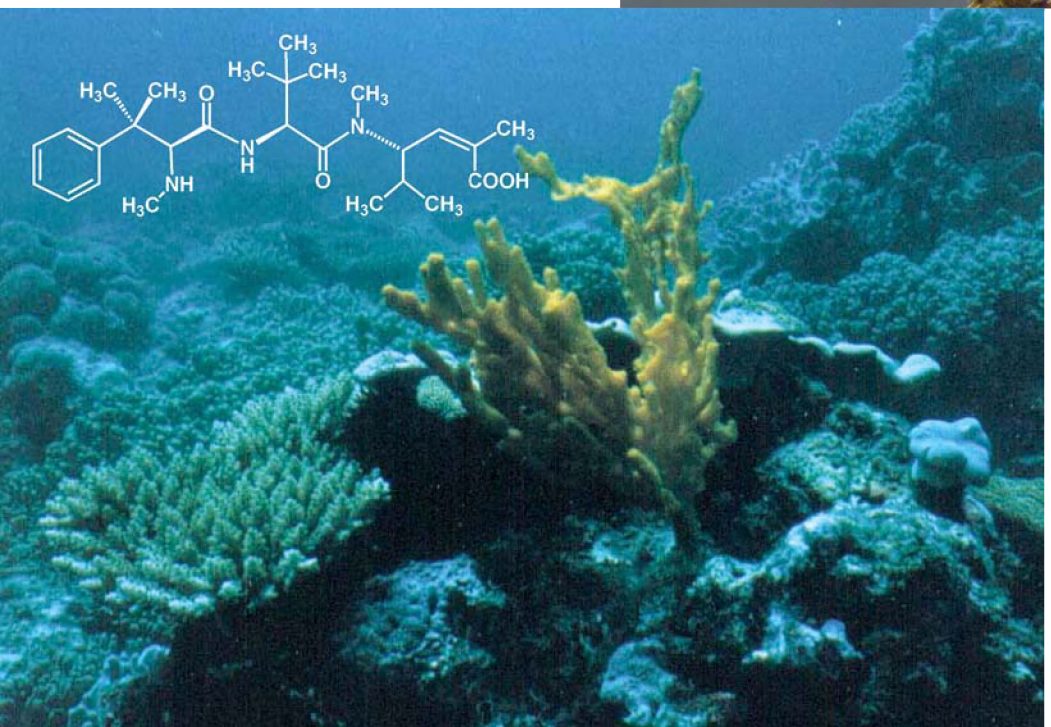


Figure 7. The Pacific sponge *Cymbastella* sp. contains highly cytotoxic peptides of the hemiasterlin class. As part of the NCI's National Cooperative Drug Discovery Grant program, a synthetic derivative, HTI-286 (shown), was developed and is now in development for the treatment of cancer. Photo courtesy R. Andersen, University of British Columbia, Vancouver, British Columbia, Canada.

derived from seawater has shown that a truly amazing complexity of microbial life exists in the sea (Venter et al., 2004). These studies have further shown that microbial diversity varies by 80 percent between samples collected only 100 miles (161 km) apart.

Clearly, new genomics tools are greatly expanding our understanding of microbial diversity of the open ocean. One of our greatest resources now appears to be deep ocean sediments. Although sediments have been known for decades to harbor over 10^9 microbial cells per cubic centimeter, it was just recently that the medically significant actinomycete bacteria (> 80 percent of all our microbial antibiotics are produced by this class of bacteria) were found there. The best example is the recently discovered and widely distributed marine actinomycete genus, *Salinispora*, which produces a diversity of novel molecules such as salinosporamide A, a potent cancer cell growth inhibitor scheduled for clinical evaluation in 2006 (Figure 8). At least 13 new groups (likely to be new genera) of actinomycete bacteria have been discovered in the last three years (Jensen et al., 2005; Stach and Bull, 2005), suggesting that these chemically rich microorganisms will be a major resource for drug discovery. When the sheer immensity of the ocean bottom is considered (70 percent of Earth's surface), it is not difficult to conceive of the importance of these resources in contributing to the badly needed antibiotics for the next millennium (Figure 9).

As time passes, marine scientists are continually illustrating the important roles symbiotic bacteria play in the biosynthesis of invertebrate-derived drug candidates. That microbes are found in symbiotic relationships with invertebrates is almost the rule in marine systems, but it has taken more than 30 years to begin to define their roles. A recent example is the discovery that the manzamine alkaloids, originally isolated from diverse sponges, are produced by an actinomycete bacterium of the genus *Micromonospora*, isolated directly from the invertebrate host (Figure 10). This is of great importance, as the manzamines are potent anti-malarial agents currently in preclinical trials (Rao et al., 2004).

It is also easy to predict that the role of combinatorial gene biosynthesis will increase as new sources for novel molecules are "manufactured" by cleverly combining and eliminating genes from whole biosynthetic gene clusters. It has also been shown that complex DNA can be extracted from environmental samples and expressed in host bacteria to generate molecules not seen before (Brady and Clardy, 2000; Brady et al., 2001; Clardy, 2005). Although this is reality in 2006, these studies are pioneering, and few complex pathways have been cloned. Although not yet routine, these new biotechnologies applied to the biosynthetically complex life in the sea are likely to create immense chemical diversity.

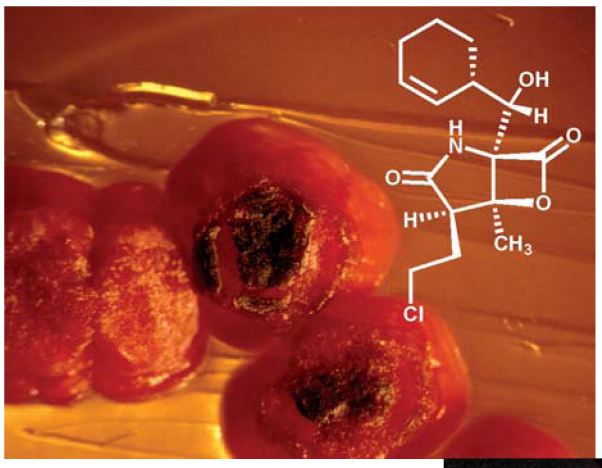


Figure 8. Close-up photograph of the new marine actinomycete, *Salinispora tropica*, the source of the potent proteasome inhibitor salinosporamide A (shown). Salinosporamide A will enter clinical trials in mid 2006 with the primary target being multiple melanoma.

Figure 9. The new actinomycete genus "Marinispora," produces novel polyene-polyols with potent antibacterial activity against drug resistant pathogens such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.

The field of marine medicine has clearly advanced from its early stages of chemical exploration to a new era in which marine-derived drugs are here. Over the next decade, we will see significant numbers of marine drugs being used in the treatment of cancer, others for intense pain and infectious diseases. There will be an expansion of these studies to focus on many therapeutic areas of growing human need. After all, if we are to return to natural products as a source for new drugs, where else might we go?

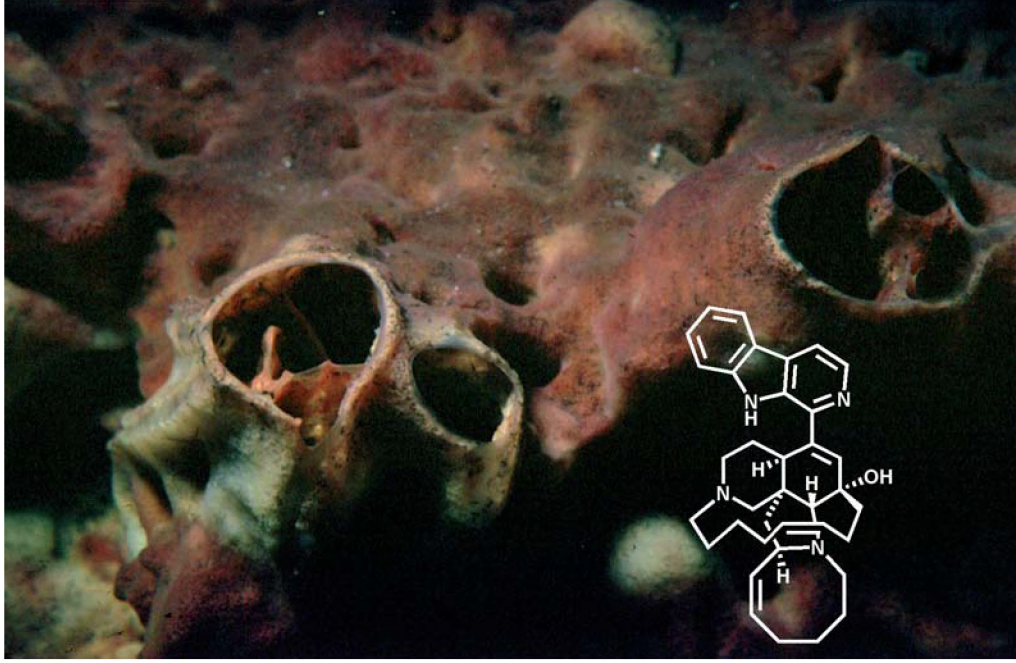


Figure 10. A close-up underwater photo of the Indonesian sponge *Acanthostrongylophora* sp. This sponge contains complex molecules of the manzamine class (manzamine A shown). The manzamines, which show potent activity against human parasites, are thought to be produced by a bacterium found within the sponge. Photo courtesy M. Hamann, University of Mississippi, Oxford, Mississippi.

ACKNOWLEDGEMENTS

I apologize to the many contributors to this field whose work I simply did not have space to describe. I am particularly grateful for the photos provided by several colleagues (see the figures for photo credit), which allowed me to adequately illustrate their excellent work.

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