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Fulfilling the promise of biotechnology

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Abstract

Genetic engineering has produced pharmaceuticals, disease-resistant plants, cloned animals and research and industrial products. While the comparably mature field of medical biotechnology now reveals its true potential, marine biotechnology is still in the realm of the future. As we explore the earth for new sources of natural chemicals, we now search the waters. Myriad organisms, most unknown to us, live there. Many produce compounds that can be commercialized, or the organisms themselves may be commercialized, through genetic engineering methods. For decades, scientists studied the ocean depths searching for unique molecules and organisms. But not until the early 1980s was there a synthesis uniting marine natural products, ecology, aquaculture and bioremediation research under the heading of marine biotechnology. As harvesting enough products from marine sources to produce sufficient amounts, even for study, is nearly impossible, we need to use genomics techniques to identify biologically active compounds. As we damage our oceanic ecosystems through pollution, overfishing and destructive fishing methods, opportunities to learn more about marine organisms and their commercial potential may be limited. Although governments and intergovernmental agencies are committed to funding and expanding oceanic research, more funding is needed to discover and study the ocean's vast, unplumbed resources.

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1. Introduction

Over the last 30 years, we have seen incredible expansion in the biological sciences. We have the ability to use genetic information to produce new pharmaceutical products, disease-resistant plants and genetically modified microorganisms for industrial and environmental use. But despite recommendations made years ago (Joint Oceanographic Institutions, 1990), marine biotechnology has been left behind. There have been splendid discoveries, nonetheless. Researchers have identified hundreds of marine microorganisms that have the potential to produce pharmaceutical compounds (Jensen and Fenical, 2000; Newman et al., 2000). They have discovered marine invertebrates that can be sources of new pharmaceuticals, cosmetics and nutraceuticals (Faulkner, 2000; Fenical, 1997; Hay and Fenical, 1996). They have experimented with new methods to raise fish, molluscs, crustaceans and algae in aquaculture (Chen et al., 1996, 1997; Neori and Shpigel, 1999, in press). Researchers have also developed new remote sensing methods to detect marine environmental changes (Lobitz et al., 2000; Pascual et al., 2000). But marine biotechnology remains a promise.

2. Brief history of biotechnology

The field of biotechnology is not new. Fermentation technology—the earliest form of biotechnology—originated with mold-fermented foods in China and beer brewing and bread making combined in Egypt (Nout, 1992).

The history of the field is strewn with milestones. The Biotechnology Industry Organization (BIO) has “A Timeline of Biotechnology” online (<http://www.bio.org/timeline/timeline.html>). This is a selective list, but it is an example of how quickly the field has progressed. The first page begins in 1750 BC with beer brewing and ends in 1911 with the discovery of the first cancer-causing virus. The second page extends through the 1950s. It includes Avery al.’s (1944) discovery of “transforming factor,” McClintock’s (1929) transposable elements and Watson and Crick’s (1953) discovery of the double helical structure of DNA. The year 1998, the last year of the timeline, takes up a full page. During the 47 years since Watson and Crick’s short and succinct paper on what is perhaps one of the most historically important scientific discoveries, the structure of the DNA molecule, the field of biotechnology has progressed from the world of science fiction to the world of science present.

In 1973, Cohen et al. (1973) produced the first recombinant DNA by cloning a gene into a bacterial plasmid. From then on, commercial biotechnology grew in quantum leaps.

We can divide biotechnology into four major market segments: biomedical, agricultural, environmental and industrial. Of all of these, the biomedical segment is growing most visibly. In 1981, the first biotechnology product, a monoclonal antibody-based diagnostic test kit, was approved by the US Food and Drug Administration (FDA). The following year, Genentech’s recombinant human insulin (rh-insulin; Humulin) was approved in the US for human use. rh-insulin is now the primary insulin on the market. BIO maintains a list of biotechnology-based pharmaceuticals in the marketplace (<http://www.bio.org>). From 1982 to 1989, 18 biotechnology-based drugs were approved by the FDA. In the 1990s, 125 drugs were approved, with 22 approved each year in 1998 and 1999. The growth in the industry is staggering. Ernst and Young (Morrison and Giovannetti, 1998) reported a total of 305 biotech drugs in Phase II/III or Phase III clinical trials for major diseases in 1999, up from a bit more than 150 such trials in 1998.

Vaccines are a potent example of the influence of biotechnology on modernization of an old technology. The beginning of vaccination was variolation, the infection of healthy people with smallpox virus through introduction of infectious smallpox scab material into the uninfected. It is unknown where and when this method was first utilized, but there is evidence of variolation in China, Europe and Africa several hundreds of years ago. By the early 1700s, variolation was introduced to the Massachusetts Bay Colony—probably via information from an African slave—and in Europe was discovered by a member of the British aristocracy who had her children variolated. Variolation probably was practiced by peasants for hundreds of years, and it became widespread in Europe and North America by the end of the 18th century (Crosby, 1993). By 1798, Edward Jenner had published his report on successful vaccination against smallpox with cowpox, leading to mass vaccinations in the early 19th century. By the end of the 19th century, immunological research in Europe led by Pasteur, Mechnikov, Koch, Lister and others resulted in diphtheria serum, rabies vaccine and animal vaccines (Mazumdar, 1993).

By the first half of the 20th century, vaccines against tetanus, diphtheria and whooping cough were developed (Salyers and Whitt, 1994), followed shortly thereafter by killed and attenuated live polio vaccines (Cohen, 2001). Although many vaccines have since followed—some, such as the *Haemophilus influenzae* type b vaccine, required molecular biology techniques to isolate the capsular polysaccharide from the bacteria and link it to a protein (Salyers and Whitt, 1994)—the first US-approved vaccine to utilize recombinant DNA technology was Merck's Recombivax-HB recombinant hepatitis B vaccine. It was initially approved in January 1987.

Our ability to adapt genetic engineering technology to vaccine development has brought us additional US-approved vaccines: against canine Lyme disease; whooping cough; and pertussis, diphtheria, tetanus and *H. influenzae* combined. Vaccines using technologies that include naked DNA particles, protein engineering, targeted immunity, novel delivery systems and even insertion of immunogens into plants, are in various stages of development (Stratton et al., 2000).

On the agricultural front, there has been tremendous progress since the market introduction of the genetically engineered Flavr Savr tomato in 1994. Ernst and Young reports that in 1998, 30% of the US soybean crop was expected to be from genetically engineered seeds (Morrison and Giovannetti, 1998). In 1998, about 30% of the US cotton and corn crops were also expected to be products of genetic engineering (Morrison and Giovannetti, 1998). It is almost impossible to purchase a processed food in the US that does not contain a genetically engineered fruit, vegetable, or grain.

Industrial biotechnology has taken a new focus, as well, yielding products that result in “clean” technologies, rather than focussing on remediating processes that may, themselves, pollute. Nevertheless, remediation continues to be improved, with use of microorganisms (both GMOs and naturally occurring ones, including extremophiles) to clean contaminated areas (David et al., 1995; Tebo, 1995). Offshore or other contamination of marine ecosystems resulting from toxic organics may be amenable to in situ remediation by naturally occurring consortia of microorganisms in sediments (Deming, 1998). Plants, too, offer useful applications in bioremediation (Blaylock et al., 1997; Huang et al., 1997).

3. The status of marine biotechnology

The commercial success stories in biotechnology are familiar. But the commercial success stories in marine biotechnology are far less familiar and far fewer. Marine biotechnology encompasses pharma-

ceuticals, agriculture, industrial applications and bioremediation. Although we are poised on the edge of a period of tremendous potential, marine biotechnology as a field is still in the realm of the future.

We define marine biotechnology as “the application of scientific and engineering principles to the processing of materials by marine biological agents to provide goods and services” (Zilinskas et al., 1995). In 1985, this author wrote, “There are several reasons for the lack of development in the area of marine pharmaceuticals...” (Colwell, 1985). The difficulties of retrieving a “sustained, reliable” harvest of marine organisms; insufficient quantities of material to allow for study completion; and difficulties culturing marine organisms in the lab were cited. Unfortunately, the same holds true today (Staley et al., 1997).

In a review of the biology of poisonous marine organisms, Mebs (1995) of the University of Frankfurt wrote, “The sea is a hostile environment for the human intruder.” Both the lack of accessibility to much of the oceans’ depths until recently and this perception of hostility may have resulted in the relatively tiny amount of knowledge we have of the ocean and sea creatures.

The oceans comprise more than 70% of the Earth’s surface, yet each drop of water taken from the ocean will contain microbial species yet unknown to humans in a 9:1 ratio. Nevertheless, that does not mean that we are not cognizant of the value of oceanic organisms. We have fished the oceans to the point where modern methods have left many fisheries irreparably damaged and marine ecosystems poised on the edge of major, and perhaps seriously adverse, change (Colwell, 1997). Historical records show that our species has been aware of the venomous nature of some sea creatures for at least 4000 years. Extracts of marine animal venoms had medicinal uses more than 2000 years ago. In the 19th and early 20th centuries, cod liver oil was a staple to “build you up.” But, it was not until nearly the middle of the 20th century that scientists began to systematically probe the oceans looking for sources of medicines and industrial products (Nigrelli et al., 1967).

World War II was an impetus to learn more about marine organisms (Nigrelli, 1944). At that time, the US National Research Council began to consider additional fish species that could be used for food. They—and the US military, whose forces ate ocean-dwelling fare worldwide—found that many species were toxic. By the early 1950s, Ross Nigrelli of the Osborn Laboratories of the New York Aquarium, New York Zoological Society, extracted a toxin from the Cuvierian organs of the Bahamian sea cucumber, *Actinopyga agassizi*. This was one of the US National Science Foundation’s (NSF) earliest funded marine biotechnology projects (Bridges, 1974). Nigrelli named the substance, which showed some antitumor activity in mice, holothurin (Nigrelli et al., 1967; Atz, 1952; Kitagawa et al., 1981). Although holothurin never was commercialized, the search for drugs from marine organisms has continued.

In 1947, Rosenfeld and ZoBell (1947) at Scripps reported on antibiotic activity from marine microorganisms found as a result of a study to determine why sea water was bacteriostatic or bactericidal to some nonmarine bacteria in culture. They identified nine species of marine microorganisms that showed antibiotic activity. “It is suggested that the sea may represent a reservoir of microbial antagonists of possible importance,” they wrote.

In the 1970s, with the advent of recombinant DNA techniques and the discovery of unique microbes living in hydrothermal vents in the ocean floor, it became clear that the application of genetic engineering to all forms of marine life comprised a synthesis, the beginnings of the field of marine biotechnology (Colwell, 1983). It extends from production of commercially and medically important chemicals from algae and marine invertebrates; to production of transgenic fish, crustaceans and molluscs for food; and genetically engineered medicines and vaccines for aquaculture. Information in the field has burgeoned. ISI’s databases indicate about 108 references related to marine biotechnology by the

early 1980s. But from 1994 to 1996 alone, Sea Grant Colleges, which are in 30 US states, produced 700 publications in marine biotechnology.

4. The Archaea

Improved technology allowing us to sample organisms on the ocean floor has yielded a different view of life. Not only are we learning of the vast diversity of organisms, from microbes through finfish that live in the oceans, we also have learned a new classification of organisms, resulting from the identification of the Archaea. Organisms now are separated into three domains: the Archaea, the Bacteria and the Eucarya (Woese et al., 1990). Many of these Archaea are extremophiles, organisms that live beyond the parameters that we had once believed formed the borders of the environmental limits of life. The domain includes the halophiles (from salt flats or extremely salty bodies of water), the thermophiles (from hot vents or hot geysers), the thermoacidic Archaea (which survive at very low pH and high temperature), and the psychrophiles that live in the cold waters of the Antarctic. But the most important value of these organisms (along with some of the Eubacteria that also tolerate extreme environments) is that their enzyme systems work at extremes. Many of the restriction enzymes used in gene splicing and cloning are products of extremophiles. These organisms' enzyme systems are adaptable for many industrial uses in high- and low-temperature or extreme pH processing. A recent US National Academy of Sciences report noted that in 1993, world enzyme sales equaled US\$1 billion, a market that was expected to grow about 10% per year (Committee on Biobased Industrial Products, 1999). Enzymes from extremophile sources will constitute a part of this market.

5. Natural polysaccharides

The field of marine natural products is already large and growing. Seaweeds are an abundant source of natural polysaccharides, many of which have commercial uses (Brant and Buliga, 1985). Algal products, such as agar and agarose have been used in the laboratory for many years as nutrient media and electrophoresis gels, respectively. Carrageenan, another algal derivative, is used as a thickener in processed food (Anon., 1991; Hansen et al., 1981). Algae are sources of vitamins, other nutrients such as docosahexaenoic acid, iodine, animal feed additives, fertilizer and pharmaceuticals (Fan, unpublished). The world market value of nori—the seaweed *Porphyra*, most familiar to us as the wrapping for sushi, but also a source of the fluorescent biochemical tag r-phycoerythrin—exceeds US\$1.61 billion/year (Chopin et al., 1999). Chitin and chitosan, polysaccharides derived from the chitinous exoskeletons of marine crustaceans, such as shrimp and crabs, are used in the food industry. They add bulk as gelling agents, and control formation of ice crystals in frozen foods (Knorr, 1984). They also have uses in agriculture as antifungals and medicine as sutures and poultices (Zilinskas et al., 1995).

6. Source of pharmaceuticals

Since the discovery of many toxic molecules in ocean creatures, it became evident that the ocean is a likely source of pharmaceuticals. Despite nearly 40 years of research into such drugs, we have

almost no approved pharmaceuticals on the market derived from marine organisms. The antiviral acyclovir and its relative AZT, along with the anticancer drug, Ara-C, are derivations of materials originally isolated from marine sponges (Newman et al., 2000). The cephalosporins were originally isolated from a pseudomarine fungus found in sewage sludge in Sardinia. One antiinflammatory substance, a partially purified pseudopterosin extracted from the Caribbean sea whip, the soft coral *Pseudopterogorgia elisabethae*, has been licensed for use in Estée Lauder's Resilience skin-care products (Faulkner, 2000; Fenical, 1997).

One of the problems in producing materials from marine sources is the inability to harvest enough of the source organism. This is not the case with *P. elisabethae*. Ten thousand pounds of this gorgonian have been harvested from the coast of the Bahamas. Researchers expect that this population, which regrows rapidly, is sustainable (Faulkner, 2000).

Many other potential products, a large number of which were discovered with the assistance of the National Cancer Institute's Natural Products Branch, are in clinical trials or earlier stages of development (Newman et al., 2000). These molecules often are secondary metabolites, substances that have no metabolic functions within the organism but are produced by the organism. We are learning that, in some cases, these compounds are produced by microbial symbionts of the host organism. Some of these are toxins that may repel and serve to protect organisms from predation. Among these are palytoxin, a potent nonprotein toxin isolated from the zoanthid, *Palythoa* sp. (Carte, 1996); okadaic acid derivatives, isolated from dinoflagellates and known to cause diarrhetic shellfish poisoning (Smart, 1995); tetrodotoxin, most well known for its presence in the Japanese puffer fish, the fugu, although present in numerous species of fish, marine invertebrates, algae and even some amphibians (Kaku and Meier, 1995); and ciguatera toxin, produced by marine protozoans that are ingested by many fish species, rendering the fishes' flesh toxic (Glaziou et al., 1995).

7. Neurotoxins

Although tetrodotoxin, one of the most potent neurotoxins known, which is found in the ovaries and liver of puffer fish, has resulted in no major pharmaceuticals to date, this marine fish extract, along with saxitoxin, a neurotoxin isolated from dinoflagellates, has formed the cornerstone of basic research on nerve function (Shimizu, 1982; Narahashi, 2000). Both toxins block voltage-gated sodium channels in neurons. Seminal studies on neurophysiology and neuropharmacology using these toxins were published beginning in 1960. Northwestern University's Toshio Narahashi, a pioneer in the field, reviewed his early studies in a recent paper (Narahashi, 2000). The existence of these two marine toxins was essential for understanding the role of sodium channels and the physiology of the action potential in nerves. Tetrodotoxin is now so critical to neuropharmacology and neurophysiology research that a Medline search revealed 282 papers citing this toxin published in 2000 from January through late October.

8. Microbial sources

With the ability to identify more marine microorganisms that are potential sources of pharmaceuticals, the number of papers citing such work has increased dramatically. Paul Jensen of the Scripps Institute of

Oceanography maintains a database of citations of novel organic compounds from marine bacteria and fungi (Fig. 1). The first citation for bacteria was in 1973. From then through the first weeks of January 2000, Jensen logged 116 citations, 90 of which date from 1990–1999. There were six citations in January 2000 alone. Citations of novel organic compounds from fungi similarly have increased in recent years (Fig. 2).

Despite this increasing number of reported discoveries from marine bacteria and fungi, there are no drugs even approaching clinical trials that are derived from any marine microorganisms.

As this author noted in 1983 (Colwell, 1983), the application of genetic engineering methods to marine science creates an opportunity for research and for the oceans to serve as sources of products. Despite advances in the identification and screening of organisms for biologically active compounds, production of sufficient amounts of the compound depends on a number of factors. One is the ability to chemically synthesize the compound. Another is the ability to raise the organism in culture (as is done with the bryozoan *Bugula neritina*, a source of the antitumor molecule, bryostatin 1). A third is the ability to harvest the organism from its natural environment. Genetic engineering techniques allow us the option of identifying the active gene, removing it from the organism and splicing it into another organism that is easier to culture (Newman et al., 2000).

This, along with the advent of rapid-screening genomics and high-throughput screening for pharmaceutical activity, is likely to result in identification of compounds from marine organisms that have potential commercial uses.

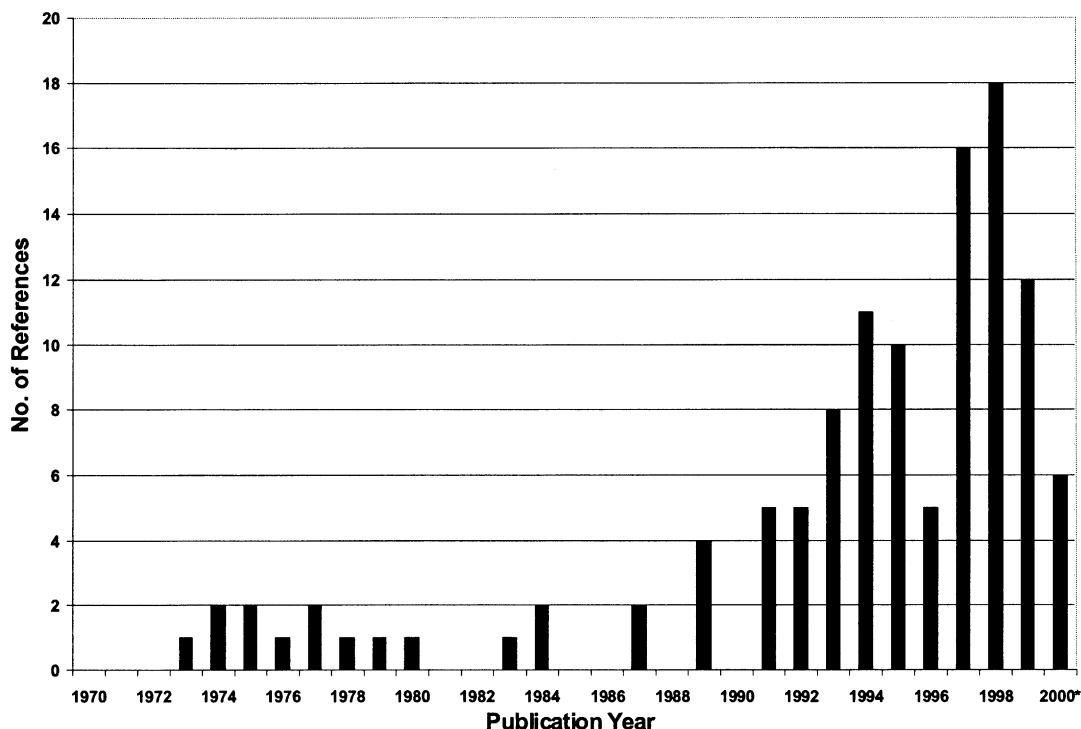


Fig. 1. Novel organic molecules reported from marine prokaryotes, cited in literature through January 5, 2000. Data courtesy of Paul Jensen, Scripps Institute of Oceanography.

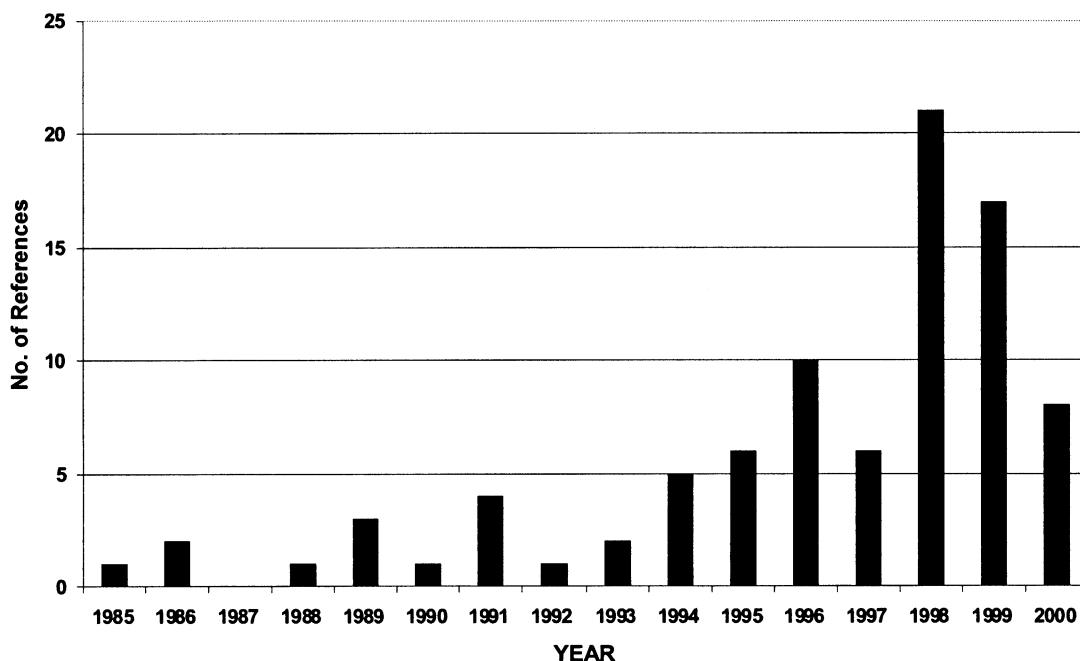


Fig. 2. Novel organic molecules reported from marine fungi, cited in literature through October 2000. Data courtesy of Paul Jensen, Scripps Institute of Oceanography.

We are finding that many of the biologically active molecules present in marine invertebrates are produced, not by the organisms themselves, but by symbiotic microorganisms (Jensen and Fenical, 1996). For example, tetrodotoxin, which was discussed earlier, has been isolated from several genera of marine bacteria (Simidu et al., 1990; Juntongjin et al., 1994; Scheuer, 1990). The question, however, is whether these or other symbiotic bacteria are responsible for tetrodotoxin secretion in vertebrates (Scheuer, 1990).

At present, there are no techniques that allow most of these microbes to grow in culture, and standard media used for nonmarine microbes may inhibit their growth (Jensen and Fenical, 1996; Jensen et al., 1996). Although modifying the media used to grow these bacteria may aid in culturability (Jensen et al., 1996), screening these microbes for genes that produce pharmaceutically active compounds may be the only way many of these marine bacterial metabolites will be identified. For example, it has been proposed that *B. neritina* is not the source of bryostatin. Rather, it has been hypothesized that the compound is manufactured by a symbiotic microorganism, possibly *Candidatus Endobugula sertula* (Haygood et al., 1999). If researchers can identify the microbial gene that produces bryostatin, that compound could, conceivably be manufactured by inserting the gene into an easily culturable bacterium, such as *E. coli*.

Ribosomal RNA (rRNA) screening techniques allow us to rapidly identify microorganisms and determine their phylogenetic relationships (DeLong, 1997). Related genomic methods will allow us to identify useful or interesting genes in these organisms (DiRita, 2000; Heidelberg et al., 2000).

Jensen and Fenical (2000) recently reviewed the status of a number of potential drugs isolated from marine symbionts. Among these is the antitumor agent alteramide A, isolated from a marine bacterium found on a sample of the sponge, *Halichondria okadai*. The compound has cytotoxic effects against some leukemia, lymphoma and human epidermal carcinoma cells. Researchers have isolated the cytotoxic

alkaloid, asperazine, from the fungus *Aspergillus niger* living on a sponge, *Hyrtios* sp. The compound also is cytotoxic to certain leukemia cells in culture. Despite the promise of such compounds, they are yet many years from development as drugs. Of the marine-organism-derived antitumor drugs in clinical trials, only three are in Phase II trials: Bryostatin 1; Ecteinascidin 743, derived from a Caribbean tunicate; and Dehydrodidemnin B (aplidine), from a Mediterranean tunicate. Others, such as Didemnin B, also from a Caribbean tunicate, were abandoned in Phase II trials as too toxic (Gordon Cragg, personal correspondence).

Molecules with possible agricultural uses have been isolated from symbiotic marine bacteria. Our laboratory at University of Maryland recently reported the isolation of a plant growth inhibitor and several plant growth promoters from a culture of bacteria isolated from *Palythoa* sp. (Cronan et al., 1998).

9. Aquaculture

Genomics will allow us to identify useful genes in fish, invertebrates and algae for maintenance in aquaculture (Alcivar-Warren et al., 1999). Production of transgenic fish through electroporation has been successfully carried out since the mid-1980s (Chen et al., 1996, 1997). Genomics promises the ability to specifically identify and insert genes that will aid in propagation and in maintaining the animals' health. Current genomics research on fish and invertebrate species that can be raised in aquaculture was recently summarized in a report on proceedings of an aquaculture genome workshop that included information on genomics of shrimp, oysters, salmonids and several freshwater fish species (Alcivar-Warren et al., 1999). Furthermore, molecular biology methods have resulted in production of new feedstocks and vaccines for aquaculture.

Integrated mariculture systems, such as those devised by Neori and Shpigel (1999, in press) and Shpigel and Neori (1996) at Israel's National Center for Mariculture, allow land-based production of valuable bivalves, shrimp and abalone in polyculture. Here, algae serve to remediate the nitrogenous pollution from the aquaculture waste. Yarish and colleagues at the University of Connecticut are taking this a step further by genetically engineering the red alga, *Porphyra*, used for remediation in aquaculture of salmonids, to better tolerate diverse habitats (Chopin et al., in press).

10. Research products

Genetic engineering methods already allow the cloning of genes from coelenterates to create a product that is extremely useful in cellular research. Originally reported on in 1962, green fluorescent protein was derived from the jellyfish, *Aequoria* sp. (Tsien, 1998) and later from the anthozoan, *Renilla reniformis*. It is used as a marker for gene expression, protein localization and tracking calcium within the cell (Tsien, 1998; Ward et al., 1980; Prendergast, 2000; Pollok and Heim, 1999). It has been "humanized" and cloned in mammalian expression vector systems.

11. Conclusions

To best utilize the resources at hand to achieve the results that marine biotechnology promises, governments must increase their involvement in marine biotechnology research. In the US, for

example, marine biotechnology research is funded mainly through the NSF, the National Oceanic and Atmospheric Administration (NOAA) and the Office of Naval Research (ONR). Smaller amounts are funded by the National Institutes of Health through the National Cancer Institute (NCI).

Despite our relatively small marine biotechnology budget, NSF has funded some highly productive work. The first sequencing of an extreme halophile, funded by NSF, was reported in October 2000 in the *Proceedings of the National Academy of Sciences* (Ng et al., 2000). In 1998, we funded the first NSF marine bioproducts center, MarBEC, a consortium on the campus of University of Hawaii that includes the University of California at Berkeley. The center's mandate is to create means to produce commercial quantities of marine bioproducts in joint ventures with industry (Zaborsky, 1999). NSF has been instrumental in funding exploration of the organisms living in Antarctic waters (McClintock and Baker, 1998). But more initiatives are needed.

We must increase our use of genomics to learn more about the oceanic environment. We need more studies of ecology, symbiosis, marine pathogens [such as this author's group's continuing work on *Vibrio cholerae* (Lobitz et al., 2000; Pascual et al., 2000; Huq and Colwell, 1996)], production of biosensors, etc. But, as we learn more about marine biotechnology and put its findings increasingly to use, we must make sure that we do not alienate the public, those who fund and support this important work. Agricultural biotechnology advances have confused and alarmed people worldwide who are unaware of the benefits of this technology (Guy et al., 2000). A recent newspaper report specifically cited negative reactions to the potential sale of genetically engineered salmon, which contain a growth gene from an arctic fish that allows the salmon to grow better in colder water (Kaufman, 2000). Part of this reaction derives from fear. Part may result from a genuine concern that we do not fully understand the potential results of inserting new genes into species planted in fields and consumed by animals and humans. However, without the new agricultural technologies, including use of genetically engineered plants and animals, the world, especially developing nations, will soon be facing food deficits. We can help citizens of the world understand these new technologies through education (Gallo-Meagher et al., 2000). We need more educational programs—from childhood to the general population worldwide. Thus, it is imperative that funds be allocated for education and outreach.

Nearly twenty years ago, this author believed the marine biotechnology revolution was within reach. From the amount of research done in the field since then and the numbers of discoveries, indeed, it remains so. But, from the numbers of new products that exist today, the results of the revolution are yet to be realized. Today we are closer to the goal of reaping the benefits from the sea's true potential, but coordinated national and international efforts and a significant infusion of funds are needed. Unlike 20 years ago, the scientific technology—already in use in biomedicine—has matured and is prepared for the successes of marine biotechnology.

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