MEDICINES FROM THE DEEP

The Importance of Protecting the High Seas from Bottom Trawling

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ABOUT NRDC

NRDC (Natural Resources Defense Council) is a national, nonprofit organization of scientists, lawyers, and environmental specialists dedicated to protecting public health and the environment. Founded in 1970, NRDC has more than 1 million members and online activists nationwide, served from offices in New York, Washington, Los Angeles, and San Francisco. For more information, visit www.nrdc.org.

ABOUT MCBI

MCBI (Marine Conservation Biology Institute) is a nonprofit organization dedicated to advancing the science of marine conservation biology and promoting cooperation essential to protecting and recovering the earth's biological integrity. Founded in 1996, MCBI is headquartered in Redmond, Washington, and has offices in Glen Ellen, California, and Washington, D.C. For more information, visit www.mcbi.org.

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EXECUTIVE SUMMARY

Although deep ocean exploration is still in its infancy, many scientists now believe that the deep sea harbors some of the most diverse ecosystems on earth. This diversity holds tremendous potential for human benefit. More than 15,000 natural products have been discovered from marine microbes, algae, and invertebrates, and this number continues to grow.[1] The uses of marine-derived compounds are varied, but the most exciting potential uses lie in the medical realm. More than 28 marine natural products are currently being tested in human clinical trials, with many more in various stages of preclinical development.[2]

To date, most marketed marine products have come from shallow and often tropical marine organisms, due mainly to the ease of collecting them. But increasing scientific interest is now being focused on the potential medical uses of organisms found in the deep sea, much of which lies in international waters. These organisms have developed unique adaptations that enable them to survive in dark, cold, and highly pressurized environments. Their novel biology offers a wealth of opportunities for pharmaceutical and medical research. This report documents the large and growing body of scientific evidence (see Summary Table) that deep sea biodiversity holds major promise for the treatment of human diseases.

Summary Table
Deep Sea Compounds in Development for Medical Use

Name	Application	Source	Depth/Location	Status	Comments
E7389	**Cancer:** non-small cell lung and other types	Sponge: *Lissodendoryx* sp.	330 ft (100 m) New Zealand	Phase I clinical trials	
Discodermolide	**Cancer:** solid tumors	Sponge: *Discodermia dissolute*	460 ft (140 m) Bahamas	Phase I clinical trials (completed)	More potent than Taxol®; works on multi-drug resistant tumors
Dictyostatin-1	**Cancer**	Sponge: Order Lithistida, Family Corallistadae	1460 ft (442 m) Jamaica	Preclinical development	Toxicity similar to Taxol®
Sarcodictyin/ Eleutherobin (related compounds)	**Cancer**	Coral: *Sarcodictyon roseum*	330 ft (100 m) Mediterranean	Preclinical development	Toxicity similar to Taxol®
Salinosporamide A	**Cancer:** melanoma, colon, breast, non-small cell lung	Microbe: *Salinospora*	More than 3300 ft (1000 m) North Pacific Ocean	Preclinical development	Will enter clinical trials in 2005; potency 35x omuralide
Topsentin	**Anti-inflammatory:** arthritis, skin irritations **Cancer:** colon (preventive) **Alzheimer's**	Sponge: *Spongosporites ruetzleri*	990–1980 ft (300–600 m) Bahamas	Preclinical development	
Orthopedic implants	**Bone grafting**	Coral: Family Isididae	More than 3300 ft (1000 m) North Pacific Ocean	Preclinical development	Reduces risk of mammalian disease

Unfortunately, this incredible undersea pharmacy is threatened by an extremely destructive fishing practice known as bottom trawling. This practice, completely unregulated in most areas of the high seas, involves bulldozing the deep ocean floor in pursuit of bottom-dwelling fish. One sweep of a bottom trawl can uproot and pulverize a thriving deep ocean ecosystem and all the unique life within it. Researchers estimate that an area of ocean floor one and a half times the size of the United States is raked by bottom trawling each year.[3] Recovery may take centuries or millennia, if it occurs at all.[4] Scientists are increasingly concerned that bottom trawling may be destroying medically beneficial species before they can be discovered.

In 2004, a group of 1,136 marine scientists from all over the world signed a statement urging the United Nations to adopt a moratorium on high-seas bottom trawling. Deep sea biodiversity in international waters represents an extraordinary resource that all nations have an interest in protecting and managing sustainably. Marine Conservation Biology Institute (MCBI) and Natural Resources Defense Council (NRDC), together with dozens of governments and conservation organizations from around the world, are calling for such a moratorium until the biodiversity of the deep sea is assessed and a regimen to manage and protect it is developed.

DEEP SEA BIODIVERSITY AND THE THREAT OF BOTTOM TRAWLING

For centuries, people believed that life in the ocean ended about 300 feet below the surface, the maximum depth to which sunlight could penetrate. In recent decades, however, advances in submersible technology have permitted scientists to explore the cold depths below, where they have discovered an extraordinary cornucopia of life previously unknown to science—cold-water corals as colorful and exotic as their warm-water counterparts, giant sponge reefs up to a mile long and 50 feet high, and a host of exotic creatures adapted to life in the cold, dark depths.

The incredible diversity of deep ocean life is linked to the fact that marine organisms have been evolving for much longer than their counterparts on land, and as a result have developed a greater breadth of adaptations. Some researchers argue that the continental slope, the steep transitional area where the shallow continental crust dives down to meet the deep ocean bottom, may be as rich in species as any habitat on earth, including coral reefs and tropical rain forests.[5]

This diversity holds tremendous potential for human benefit. More than 15,000 natural products have been discovered from marine microbes, algae, and invertebrates, and this number continues to grow.[6] The uses of marine-derived compounds are varied. For example, deep-water “glass sponges” form silica-based structures that may improve the function of fiber-optic cables,[7] and similar sponges are beginning to provide insights into bone regeneration.[8] Marine-derived compounds are used in a variety of consumer products, including skin creams, hair treatments, and cosmetics. However, the most exciting potential uses for marine organisms lie in the medical realm. More than 28 marine natural products are currently being tested in human clinical trials, with many more in various stages of preclinical development.[9]

To date, most marketed marine products have come from shallow and often tropical marine organisms, due mainly to the ease of collecting them. But scientific interest is now being focused on the potential medical uses of deep sea organisms, which have developed unique adaptations that enable them to survive in dark, cold, and highly pressurized environments. Their unusual characteristics offer unique pharmaceutical opportunities, making them the subject of considerable excitement in the scientific community.

Unfortunately, this incredible potential undersea pharmacy is threatened by an extremely destructive fishing practice known as bottom trawling. This fishing method drags large weighted nets across the ocean floor to catch fish that dwell on or near the bottom. Weighted nets act like bulldozers, ripping up sediments, upending boulders, pulverizing fragile corals and sponge fields, and crushing, burying, or exposing to predators organisms that cannot move out of the path of the net. In the Tasman Sea, for example, bottom trawlers fishing for orange roughy in 1997 pulled up an average of 10 tons of coral per tow. In that year, an estimated 10,000 tons of coral were destroyed in the capture of 4,000 tons of fish.[10] By some estimates, nearly 15,800 square miles (40,500 square kilometers) of ocean floor are trawled per day around the globe.[11]

The unique characteristics of deep sea organisms make them exceptionally vulnerable to this type of disturbance. The deep sea is colder, darker, and less nutrient-rich than is the ocean surface, and as a result, deep sea life tends to be exceedingly slow-growing and late to mature. Deep sea fish such as orange roughy live more than a century,[12] and deep sea corals much longer—5,000 years or more.[13] One sweep of a bottom trawl can destroy an ecosystem hundreds or thousands of years in the making. Recovery may take centuries or millennia, if it occurs at all.[14]

Bottom trawl fishing in the deep ocean is perhaps the single most important threat to global marine biodiversity.[15] Scientists are concerned that species and ecosystems are being destroyed by bottom trawling before their potential can be tapped. As part of a global campaign to generate support for a moratorium on deep sea bottom trawling, Marine Biology Conservation Institute (MCBI) and the Natural Resources Defense Council (NRDC) have prepared the following report documenting the large and growing body of scientific evidence that deep sea biodiversity holds major promise for treating common human diseases.

CANCER-FIGHTING COMPOUNDS FROM THE DEEP

The majority of marine-derived compounds are obtained from either microorganisms or stationary bottom-dwelling organisms such as corals, sponges, and tunicates. Because stationary organisms cannot evade predators through movement, they rely heavily on chemical defense mechanisms to protect themselves.[16] These mechanisms generate compounds that frequently show significant bioactivity, or effects on living cells or organisms, such as those which cause human ailments.

Two compounds originally isolated from deep sea organisms are now in human clinical trials as anticancer compounds. Several others are in preclinical stages and show considerable promise.

E7389

This compound is a cell-killing derivative of halichondrin B, one of a number of compounds originally isolated in 1985 from the Japanese sponge *Halicondria okadai*. The deep sea sponge *Lissodendoryx* sp., which occurs at depths near 330 feet (100 meters) in waters surrounding New Zealand, was later discovered to contain halichondrins in greater concentrations than shallow-water species.[17] Working with halichondrins from these deep sea sponges, researchers from Massachusetts-based Eisai Pharmaceutical, in conjunction with the National Cancer Institute, developed E7389, a synthetic compound that is currently in its first phase of human trials (Phase I) for the treatment of non-small cell lung cancer and other cancers. The drug functions by disrupting cell division in a manner similar to that of Taxol®, a widely used anticancer drug isolated from the bark of the Pacific yew tree.[18]

Discodermolide

Isolated from the sponge *Discodermia dissolute*, found near depths of 140 meters, discodermolide is one of the most promising natural products discovered to date. Originally found in the Bahamas in 1990 by scientists from Harbor Branch Oceanographic Institution, discodermolide interferes with dividing cells in a manner similar to Taxol®. Discodermolide has been shown to be more potent than Taxol® and is being tested for use against solid tumors.[19] The compound works successfully on multi-drug-resistant tumors and shows activity against Taxol®-resistant tumors.[20] Discodermolide has been licensed for further development to the pharmaceutical company Novartis and recently completed Phase I clinical trials.[21] Harbor Branch is continuing to explore several other promising compounds also isolated from *Discodermia dissolute* and other *Discodermia* species.[22]

Dictyostatin-1

Dictyostatin-1 is an anticancer compound in preclinical development. The compound was originally isolated in 1993 from a shallow-water sponge in the *Spongia* genus, which lives off the coast of the Republic of Maldives. Though the compound showed great promise in the lab, not enough material was available to continue further work. A 2003 Harbor Branch expedition collected a sponge from the order Lithistida (family Corallistadae) at a depth of 442 meters off the coast of north Jamaica; when the active compound from this species was identified, it was found to be dictyostatin-1. Experiments that have been reported so far indicate that the compound may work similarly to Taxol®, but may be more potent.[23] Work on this substance is continuing at Harbor Branch.

Sarcodictyin/Eleutherobin

Sarcodictyin was first reported in the late 1980s from the Mediterranean coral *Sarcodictyon roseum*, found at depths of up to 100 meters, but no information as to its bioactivity was reported at that time. Several years later, a similar compound called eleutherobin, which showed Taxol®-like activity, was isolated from a shallow-water *Eleutherobia* species in western Australia. Further work showed that these two compounds had a similar mode of action. Synthesis work by chemists at Memorial Sloan-Kettering and by K.C. Nicolaou at the Scripps Research Institute produced a series of closely related molecules.[24] Additionally, it was determined that eleutherobin could be produced by aquaculture using a Caribbean sponge species used in the ornamental aquarium trade.[25] Both sarcodictyin and eleutherobin are in preclinical development stages.

Salinosporamide A

Salinosporamide A, isolated from the microbe *Salinospora* and collected at depths of more than 1,000 meters, exhibits strong cytotoxicity against melanoma, colon cancer, breast cancer, and non-small cell lung cancer.[26] It also shows a potency 35 times greater than that of omuralide, a powerful anticancer agent with a new way of controlling cancer cell growth. Salinosporamide A will enter human clinical trials in 2005.[27]

OTHER PROMISING DEEP SEA PHARMACEUTICALS

Compounds derived from non-deep-sea marine species have shown potential in treating Alzheimer's disease, asthma, pain, and viral infections, among other human ailments. Ziconotide, for example, also known as Prialt®, was isolated from the marine snail *Conus magus* and recently approved by the FDA to treat pain.[28] The potential for similar applications also exists for compounds isolated from the deep sea. For example, the compound topsentin, a substance isolated from the deep-water sponge *Spongosporites ruetzleri*, which lives at depths of 990 to 1,980 feet (300 to 600 meters), shows promise as an anti-inflammatory agent to treat arthritis and skin irritations. Topsentin is also being investigated as a treatment for Alzheimer's disease and to prevent colon cancer. It is currently in preclinical evaluation.[29]

DEEP SEA CORALS IN BONE GRAFTING AND COLLAGEN SUBSTITUTION

Bone grafts to help repair fractures are the second most common medical transplant, after blood transfusions, in the United States. The procedure can be expensive and painful, and it sometimes leads to complications such as infection and tissue rejection. As a result, bone substitutes have long been explored as replacements for donor grafts.

Natural coral has been used as a bone substitute for more than 10 years in orthopedic, trauma, craniofacial, dental, and neurosurgeries. Corals have a structure similar to that of human bone, with a hard outer sheath and a spongy inner core.[30] Even if coral is not used at the site of the original injury, it can be used to replace bone harvested from the patient at the donor site, making it possible to reharvest bone later at the same site if necessary.[31] Coral bone substitutes have enormous potential, both in their natural and hybrid, synthetic forms.

At present, the tropical coral genera *Porites*, *Alveopora*, *Acropora*, and *Goniopora* are being used as bone substitutes; these are the only families known to have the correct pore diameter and the ability to connect properly with bone.[32] However, Hermann Ehrlich of the Max-Bergmann Center of Biomaterials at Dresden University of Technology in Germany and colleagues have had success using bamboo corals from the family Isididae, genera *Keratoisis* and *Isidella*.[33] Bamboo corals are often found at depths of more than 1,000 meters.[34] These corals have jointed axes made of bony calcareous structures alternating with nodes made of a protein-based material called gorgonin, giving the skeletal structure of the coral an appearance that resembles fingers. The skeletal structure and dimensions of bamboo coral are almost identical to those of bone. Ehrlich and colleagues have used that natural coral structure to successfully synthesize bone analogs.[35] The establishment of biotechnological approaches for the cultivation of bamboo corals will open a new and unique path for the development of natural bone implants.

Gorgonin is of interest to scientists for two reasons. First, it possesses chemical groups that are responsible for crosslinking and hardening structural proteins in nature. Second, it closely resembles both keratin, which forms the basic structure of hair and nails, and collagen, which is an important component of bone. Collagen is currently used in many biomedical applications, such as controlled release of medicines, scaffolding for tissue engineering, and other biomaterial applications. Cattle tissue is currently the main source of collagen, but the possibility of transmission of diseases from cattle tissue to humans makes marine animals a safer alternative.[36] Research using sponges as a direct collagen source has shown promise,[37] but understanding the mechanism by which gorgonin is formed by bamboo corals and other marine organisms will provide a model for the creation of a synthetic collagen-like material, ideally by a process that can take place at low-pressure and low-temperature conditions similar to bamboo coral's natural environment. This work is currently being explored by Ehrlich and colleagues.

NEW RESEARCH ON DEEP SEA MICROBES

Sponges and symbiotic microbes

Sponges harbor enormous numbers of microorganisms such as bacteria, cyanobacteria, and fungi, amounting to as much as 50 percent of the sponge's biomass.[38] For example, 50 percent of the cellular volume of the Australian tropical sponge *Dysidea herbacea* was shown to be composed of the cyanobacterium *Oscillatoria spongeliae*.[39] The nature of the relationship between the microbes and the host organisms is not fully understood, though it has now been proved that in at least some cases, the associated microorganisms are responsible for the defensive chemicals produced by sponges.[40] This finding increases not only the value of sponge ecosystems as sources of pharmaceutical applications but also the possibility of sustainably producing important compounds, because the microbes can be utilized more readily, efficiently, and sustainably than the hosts.

Scientists have discovered elevated microbial populations in many sponge species. For example, the sponges of the Lithistid family, a rare group discovered at depths of 300 to 600 meters off the Florida coast as well as in the shallow waters off Japan, have elevated microbial populations that are exceptionally bioactive.[41] Lithistid sponges are the source of a large variety of compounds, including the drug candidate discodermolide.

Deep sea sediment microbes

With 1 billion living cells per cubic centimeter of seafloor sediment, the ocean floor may be the next major source of pharmaceuticals. Scientists such as Craig Venter and colleagues have used new cloning techniques to show that microorganism diversity in the deep ocean greatly exceeds previous estimates.[42] Scientists at Scripps have shown that the ocean floor is nearly boundless in its potential as a source of bioactive chemicals, discovering that genetically identical organisms living in different environments produce a host of differing chemical defense compounds.[43] The discovery of novel strains and compounds is limited only by scientists' ability to reach them. Currently they have been able to sample to depths of 495,000 feet (1,500 meters).

Microbes can be used more readily, efficiently, and sustainably than can animals such as corals and sponges. Creating aquaculture operations for larger organisms can be expensive, time consuming, and space intensive, and the environmental impacts from continued natural harvest are often high. Microbes, however, can be harvested quickly and more cost-effectively, with little impact on the natural environment, if they can be cultured in large quantities.

Actinomycete bacteria, among the most common microbes on the planet, are the source of almost 70 percent of the world's naturally occurring antibiotics.[44] The discovery of most of these antibiotics stemmed from 60 years of research on soil-dwelling actinomycetes,[45] which are as yet unparalleled in their ability to produce diverse chemical compounds, including clinically important antibiotics such as actinomycin, streptomycin, and novobiocin.[46] Over the past 20 years or so, however, the rate of discovery of novel compounds from soil ecosystems has dropped drastically. This drop-off has led to the exploration of new environments and new means of identifying microbes in the search for novel antibiotics and novel actinomycete strains.[47] Scientists have been aware of the existence of actinomycetes in the marine realm since at least 1969.[48] However, the collective scientific assumption was that marine actinomycetes were of terrestrial origin and had little potential to yield novel pharmaceutical compounds. Over the past decade, scientists from the Scripps Institution of Oceanography have been exploring the oceans as a previously ignored source of actinomycete diversity and have thus far isolated more than 60 new chemical compounds from actinomycetes.[49] Even more remarkably, they have characterized 10 new genera of microbes (the last new terrestrial genus was discovered in the 1980s),[50] including the genus *Salinospora*, from which they have isolated more than 2,500 new strains.[51] *Salinospora* microbes have been isolated in large numbers from diverse ecosystems, including tropical and subtropical marine locations such as the Caribbean Sea, the Red Sea, the ocean waters around Hawaii, and the Sea of Cortez.[52] Scripps scientists have found actinomycetes and other novel microbes at depths of up to 495,000 feet (1,500 meters), a further indication of the group's diversity and level of adaptation to the marine environment.[53]

The difficulty of culturing marine bacteria was once considered one of the greatest roadblocks to utilizing marine microorganisms in research. Fewer than 0.1 percent of the microorganisms known to exist can be cultured and thoroughly studied.[54] However, by increasing the cultivation time and reducing the nutrient content of growth media to mimic ocean composition, scientists at Scripps have now been able to culture more than 50 percent of the bacteria observed in some samples.[55]

New techniques have also been developed for detecting novel microorganisms, even in well-studied habitats such as soils, and for using the compounds these microbes produce. Large groups of microorganisms that are impossible to culture can now be studied genetically by isolating segments of their DNA and cloning them into readily cultured organisms such as *Escherichia coli*.[56] The clones are then screened for bioactivity. This technique has shown researchers that microbial diversity is much greater than originally thought.[57] It greatly expands the number of microorganisms that can be used for natural products research and eliminates many of the development stages previously needed to carry out commercial production of bioactive compounds.[58]

CONCLUSION

The deep sea is a potentially huge source of medically important compounds, a source that science has only begun to explore. This pharmaceutical cornucopia should be protected from destructive fishing practices like bottom trawling until the organisms can be identified and assessed. Because much of the deep sea lies beyond the zones of national jurisdiction, it is up to the international community to act to protect and manage the deep sea so that all mankind can benefit. An immediate moratorium should be placed on high-seas bottom trawling until enforceable regulations to identify and protect these sensitive ecosystems are in place.

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