
What lies underneath: Conserving the oceans' genetic resources

Jesús M. Arrieta^{a, *}, Sophie Arnaud-Haond^b, and Carlos M. Duarte^a

^a Department of Global Change Research, Institut Mediterrani d'Estudis Avançats, Consejo Superior de Investigaciones Científicas (CSIC)- Universitat de les Illes Balears (UIB), 07190 Esporles, Mallorca, Spain; and

^b Institut Français de Recherche sur la Mer (IFREMER)-Department "Étude des Écosystèmes Profonds" - DEEP, Centre de Brest, BP 70, 29280 Plouzané Cedex, France

*: Corresponding author : Jesús M. Arrieta, email address : txetxu@imedea.uib-csic.es

Abstract:

The marine realm represents 70% of the surface of the biosphere and contains a rich variety of organisms, including more than 34 of the 36 living phyla, some of which are only found in the oceans. The number of marine species used by humans is growing at unprecedented rates, including the rapid domestication of marine species for aquaculture and the discovery of natural products and genes of medical and biotechnological interest in marine biota. The rapid growth in the human appropriation of marine genetic resources (MGRs), with over 18,000 natural products and 4,900 patents associated with genes of marine organisms, with the latter growing at 12% per year, demonstrates that the use of MGRs is no longer a vision but a growing source of biotechnological and business opportunities. The diversification of the use of marine living resources by humans calls for an urgent revision of the goals and policies of marine protected areas, to include the protection of MGRs and address emerging issues like biopiracy or benefit sharing. Specific challenges are the protection of these valuable resources in international waters, where no universally accepted legal framework exists to protect and regulate the exploitation of MGRs, and the unresolved issues on patenting components of marine life. Implementing steps toward the protection of MGRs is essential to ensure their sustainable use and to support the flow of future findings of medical and biotechnological interest.

Keywords: marine protected areas, marine reserves, natural products, gene patents, law of the sea

The protection of marine areas to manage fisheries in a sustainable manner has been in place for centuries, since Polynesian cultures closed areas to fishing to protect breeding grounds and allow recovery from overfishing (1), but the usefulness of no-take areas was conclusively demonstrated by the recovery of fish stocks in World War II mine fields in the North Sea closed to fisheries (2). Marine protected areas (MPAs) have since emerged as key instruments to protect fish stocks and other living resources from overexploitation (3) and have expanded to exceed 5,000 locations, covering about 0.7% of the oceans (4).

The advent of biotechnology has broadened human use of biological resources far beyond food to include other valuable products, such as flavors, fragrances, enzymes, and medicines. Although terrestrial plants have been used as medicines for millennia and still support the needs of 80% of the world population (5), the use of marine biological resources for purposes other than food is now blooming. The discovery of organisms containing molecules and genes of commercial interest is growing in parallel to the exploration of marine biodiversity. Historically, MPAs have been set up for the conservation of general marine biodiversity or for the preservation of fisheries resources (6), but the increasing use of marine species as sources of genetic resources calls for a reassessment of the scope of MPAs to include the protection of these key emerging resources.

Here, we report on the accelerating rate of discovery of marine genetic resources (MGRs) and the associated emerging challenges for the shared use of the oceans and the conservation of the resources they contain (7). We do so based on the examination of patterns in the use of marine organisms to derive natural products and gene-associated patents, using data derived from inventories of natural products (SI Text) and data extracted from GenBank (8), respectively. We then discuss the need to regulate the use of these emerging marine resources and the leading role that MPAs could have in the protection of MGRs.

1. Marine Biodiversity and the Ocean's Bounty of Genetic Resources

Marine species make up about 9.7% of total named species (9) (Table 1), a proportion comparable to the share of research effort on biodiversity allocated to marine systems (10) and the fraction of marine species among those described each year (9). However, the most surprising discoveries in biodiversity in the past decades have taken place in marine systems, including the discovery of a whole ecosystem based on chemosynthesis in hydrothermal vents in 1977 (11); the description of a previously unnoticed metazoan phylum, the Loricifera, discovered in 1983 (12); and the discovery in the 1980s of the marine phototrophic prokaryote *Prochlorococcus*, which turned out to be the most abundant photosynthetic organism on Earth (13). Recent coordinated international efforts, such as the Census of Marine Life (14) and the World Register of Marine Species (15), are propelling the growth of the inventory of named marine organisms at a rate of 0.93% per year (Fig. 1A). This growth is dwarfed by a rapid increase in the inventory of marine natural products and genes of commercial interest derived from bioprospecting efforts. The number of natural products described from marine species is growing at a rate of 4% per year (Fig. 1B and Table 1), which is much faster than the rate of species discovery, because many species yield multiple natural products. Indeed, about 18,000 natural products have been reported from marine organisms belonging to about 4,800 named species (16) since the initial reports in the 1950s.

The growth of patents that include genes of marine origin is even faster. The patent (PAT) division of GenBank (8) (release 165) lists more than 5 million records of DNA sequences deposited in different patent offices worldwide. Most of these sequences belong to a few selected species, mainly humans, pathogens, and model organisms. Although the patent inventory in GenBank is not exhaustive, the reported sequences include DNA from 3,634 named species. This register includes 4,928 nonredundant marine gene sequences derived from 558 distinct named marine species (Table S1). Since 1999, the number of marine species with genes associated with patents has been increasing at an impressive rate of about 12% species per year, which is more than 10 times faster than the rate of description of marine species (Fig. 1A). This is, however, an underestimate, because cloning and sequencing techniques allow description and patenting of genes of species yet to be named or even discovered.

The 18,000 marine natural products reported in Table 1 comprise about 10% of total natural products known (17), which is in good agreement with the share of marine species in the total inventory of named species (Table 1). In contrast, the proportion of named marine species with genes included in patents (28%) far exceeds the contribution of marine organisms to the total inventory of named species (10%) (Table 1). Wild marine species used as source of natural products outnumber by up to 18-fold those ever domesticated, while the number of species included in patent applications is growing almost 4 times faster than the number of domesticated marine species (18) (Fig. 1). Thus, appropriation of MGRs is progressing much faster than the already impressive rate of domestication for aquaculture (19).

2. Taxonomic Provenance of MGRs

The taxonomic origin of MGRs covers the entire breadth of the Tree of Life, from Archaea to vertebrates (Fig. 2 and Fig. S1), in contrast to the limited taxonomic range of domesticated species. Although the bulk of the Earth's metabolic diversity resides in prokaryotic organisms (18), natural products of marine origin are almost entirely (97%) derived from eukaryotic sources. The reason for this apparent paradox is that marine natural products have been mostly derived from large sessile organisms, which are easily collected and provide relatively large amounts of biomass for screening of natural products. Sponges alone are the source of 38% of all reported marine natural products, followed by cnidarians (20%), tunicates (under Chordata, 20%), and red algae (Rhodophyta, 9%). However, a major prokaryotic contribution is compatible with these estimates, because a significant fraction of sponge biomass, for example, is composed of symbiotic microbes, which are increasingly identified as the source of the secondary metabolites contributing the natural products attributed to their host (20, 21). The share of marine natural products of microbial origin may expand rapidly in the future, as demonstrated by the 600% increase in the number of marine natural products of microbial origin reported in 2007 relative to the average figure for the period 1965–2005 (22).

The taxonomic provenance of the marine sequences in patents is quite different from that of marine natural products, because more than a third (39%) of the marine species in the PAT division of GenBank are prokaryotes (bacteria and Archaea), contributing 42% of the marine genes included in patents, in contrast to the ample dominance of eukaryotes among the marine species domesticated for food or used to derive natural products. Moreover, the percentage of described species being a source of patents is much larger for prokaryotes as compared with eukaryotes for both terrestrial and marine organisms (Table 1). Chordates (mainly fish), mollusks, and cnidarians are the major eukaryotic sources of gene sequences

in patents, contributing, respectively, 17%, 15%, and 9% of the marine species yielding patented gene applications (Fig. 2 and Fig. S1).

3. Applications and Prospects for MGRs

Marine ecosystems are particularly suited for bioprospecting. Our survey indicates that marine species are about twice as likely to yield at least one gene in a patent than their terrestrial counterparts (Table 1), and it is estimated that the success rate in finding previously undescribed active chemicals in marine organisms is 500 times higher than that for terrestrial species (23).

The applications of genes of marine organisms patented thus far range widely, with a prevalence of applications in the pharmacology and human health (55%), agriculture or aquaculture (26%), food (17%), or cosmetics (7%) industry and an emerging and growing number of applications in the fields of ecotoxicology, bioremediation, and biofuel production (Fig. 3). Many of the patents are related to the production of enzymes and other reagents for molecular and cell biology applications (29%) and to the genetic engineering (modification) of organisms (48%).

Current applications of patents associated with genes of marine origin are mostly based on a few specific properties of marine organisms. About 8% of the patents relate to the use of polyunsaturated fatty acids, which are present in high quantity and diversity in marine organisms. These are components of dietary supplements that deliver health benefits to humans and can alleviate a broad range of diseases (24). Another major cluster of marine patents involves fluorescent proteins with applications in biomedical research and cell and molecular biology (25). Their importance is illustrated by the 2008 Nobel Prize in Chemistry awarded to Shimomura, Chalfie, and Tsien for the discovery and development of GFPs, originally described from the jellyfish *Aequorea victoria*. Many of the patents are associated with genes of marine organisms inhabiting extreme environments, such as hydrothermal vents and polar oceans. The adaptation of enzymes of hydrothermal vent organisms to very high operating ranges of temperature (>80 °C) and pressure (>100 bar) allow the use of these “extremozymes” in the transformation of substrates of biotechnological interest to proceed under the harsh conditions imposed by some industrial processes. Applications of thermophilic and barophilic (pressure-loving) enzymes include the liquefaction of starch for biofuel production, the use of inteins for the safe production of toxic proteins, and the use of thermostable enzymes in molecular biology (26). Marine organisms from polar areas are the source of psychrophilic (cold-loving) enzymes, which present high activity at low temperatures. These enzymes allow processing of heat-sensitive substrates and products, such as food, or the avoidance of expensive heating steps in some processes. Some applications of psychrophilic enzymes include the use of proteases, amylases, and lipases in the formulation of detergents active at low temperatures or the use of cod pepsins for the production of caviar and descaling of fish. Other applications of cold-adapted enzymes include proteases for meat tenderizing or for the efficient skinning of squid and the use of β -galactosidases for the elimination of lactose from milk (27).

The blooming of marine patents and patent applications associated with MGRs is largely a result of recent technological advances in exploring the ocean and the genetic diversity it contains. Advances in technologies for the direct observation and sampling of the deep ocean, including the development of submersibles and remotely operated vehicles, opened the deep and hitherto unexplored areas in the high seas to bioprospecting. Parallel developments in molecular biology, including high-throughput sequencing, metagenomics,

and bioinformatics, are greatly accelerating our capacities to explore and make use of the genetic resources of the ocean, even before the source organisms are discovered in some cases. The continued improvement in these technologies is facilitating the human appropriation of the genetic resources of the oceans, which is already evident in the very rapid growth of patents that include genes and natural products of marine organisms presented here (Fig. 1B).

Bioprospecting of marine resources only requires the collection of a very limited amount of biomass for the initial gene or product discovery. Therefore, bioprospecting does not generally involve threats to biodiversity comparable to the large biomass removals involved in harvesting of marine resources for food (28). This is especially true for gene finding, where a small amount of biomass can provide enough DNA for endless replication by cloning or PCR. However, in the case of natural products, when a promising drug candidate is found, a second more substantial harvest may be needed to collect the several grams needed to test the drug's suitability in clinical studies. Examples of these needs for large biomass collections are the anticancer drug ecteinascidin 743, obtained from the tunicate *Ecteinascidia turbinata* (1 g in 1,000 kg wet weight), the cytostatic halichondrin B from *Lissodendoryx* sp. (300 mg in 1,000 kg) (29), or the bryostatins from the bryozoan *Bugula neritina* (1.5 g in 1,000 kg) (30). Although total synthesis of these substances has been successfully demonstrated, it was deemed economically unviable (29), resulting in the need for large collections of wild biomass. A survey on the feasibility of *Lissodendoryx* sp. harvests revealed that only small quantities of this sponge can be collected despite its relatively good population recovery after dredging. On the other hand, more than 12,000 kg of *B. neritina*, enough to support all preclinical and clinical trials, were recovered from docks and pilings where this fouling organism is commonly found, with no detectable impact on the populations (30). These results demonstrate the need for careful assessment of the impact of harvesting and the capacity of the species for postharvesting recovery before attempting large biomass harvest. Although these large collections may be feasible at the research stage, successful launch of any of these substances as therapeutic agents would require a few kilograms per year of the active principle. Matching such demand would require harvesting about 106–107 kg (31) of the corresponding organism, which is clearly unsustainable, given their limited distribution. However, commercial extraction of wild resources may be possible in some instances. The pseudopterosins found in the Caribbean octocoral *Pseudoptero-gorgia elisabethae* are used in the cosmetic industry for their antiinflammatory and analgesic properties. Large wild harvests of *P. elisabethae*, estimated at 13–20 tons per year, have been conducted in the Bahamas for over a decade (32). The successful exploitation of these octocorals has been made possible by a combination of two factors: (i) a careful collection strategy that involves manually clipping part of the coral and allowing the central branches to recover for 2–3 y and (ii) regulation by means of an export limit set by the Bahamas Department of Marine Resources (32).

Wild harvests of marine organisms are undesirable from a conservational point of view because it is not always possible to predict their impact accurately. Anyway, many of these large biomass collections can be avoided when alternative production schemes are developed. Cost-effective commercial scale production in aquaculture has been demonstrated for *E. turbinata*, *B. neritina*, and several sponges (31). Moreover, a dinoflagellate symbiont of *P. elisabethae* has been found to be the source of pseudopterosin (33), and bryostatins have recently been attributed to an uncultured bacterial symbiont of *B. neritina*, indicating that production in simple microbial cultures may be possible in the future. Also, the limitations in the supply of halichondrin B have been resolved by the synthesis of simplified artificial analogues (34). These developments indicate that the exploitation of

scarce MGRs can be pursued in a sustainable manner with little impact on the populations of the source organism in many cases.

Many potential sources of genes and natural products become available every year, because the rate of discovery of previously undescribed marine species remains high (Fig. 1A). A complete inventory of marine species may require a further 250–1,000 y at current rates of discovery (9), projecting opportunities for discovery of MGRs well into the future. The prospect for unique findings is huge, particularly in the microbial realm, as illustrated by recent studies reporting 1.2 million previously undescribed gene sequences using cultivation-independent sequencing techniques on a single cubic meter of water from the Sargasso Sea (35) and 6 million previously undescribed proteins and 811 distinct prokaryotic ribotypes (a proxy for species) from a series of 45 surface seawater samples (36). Impressive as they are, these numbers are likely gross underestimates of the true potential for discoveries because the inclusion of rare and normally undetected prokaryotes may increase present estimates of marine microbial diversity by one to two orders of magnitude (37).

4. MPAs and the Conservation of MGRs

Very little is known about the conservation status of most of the species used so far as sources of MGRs. The Red List of Endangered Species of the International Union for Conservation of Nature (IUCN) (38), one of the foundations for determining and validating conservation priorities, contains data about only 36 of the 340 marine eukaryotic species reported as a source of genes included in patents, of which 10 appear as “data deficient,” 2 as “endangered,” 6 as “vulnerable,” and 7 as “near threatened.” Thus, 8 of the 36 marine species assessed so far are threatened, and 7 of them are close to qualifying as threatened or likely to be threatened in the near future. Although current Red List coverage of marine species is biased toward fish and other large metazoans, efforts are in progress to expand coverage from the actual number of 2,331 (38) to about 20,000 species by 2012 (39), which will likely result in a greater number of threatened species among those listed as a source of genes and natural products. Nevertheless, the data shown here illustrate the need to identify threats and determine conservation priorities for MGRs.

We are not aware of any conservation measures ever taken to protect prokaryotes, which comprise a large share of the MGRs described in this paper. The most extended view is that microbes, in general, are not likely to be endangered because of their sheer numbers, fast growth, and potential global dispersion (40, 41). However, some microbes are constrained to very particular environments, which make them sensitive to the same threats faced by their milieu. Examples include symbiotic microbes, which are likely to perish along with their hosts, or the obligate psychrophiles dwelling in Arctic Sea ice and its surrounding waters, which are unable to cope with warmer temperatures, and are therefore threatened by global warming. Thus, some of the prokaryotes sourcing natural products and genes of economic interest may be confronting a much higher risk for extinction than hitherto assumed (40, 41).

The exploitation of MGRs has the potential to be a sustainable process delivering considerable wealth and business opportunities. The global market for marine biotechnology was estimated at US \$2.1 billion in 2002, increasing at a rapid 9.4% from the previous year (23). However, these practices will only be sustainable if based on sound internationally accepted governance and conservation mechanisms, which are lacking as yet and must be urgently developed. Prospects are indeed jeopardized by the global deterioration of marine ecosystems by direct and indirect human pressures conducive to biodiversity loss (9, 38, 42)

and the associated loss of potential genetic resources. The unresolved legal and ethical issues associated with bioprospecting and the global protection of biological resources allocated beyond national jurisdictions also represent major obstacles for the sustainable exploitation of MGRs.

MGRs of economic interest are deemed to be particularly abundant in biodiversity hot spots, such as coral reefs and sea mounts, and in extreme environments, such as polar and hydrothermal vent ecosystems. Unfortunately, coral reefs, sea mounts, and marine polar environments are threatened. Coral reefs are experiencing a steep global decline, which is forecasted to be aggravated further by climate change and ocean acidification (43, 44). Polar ecosystems experience some of the fastest warming rates on the planet, particularly in the Arctic (45), leading to a loss of sea ice and warming of seawater above the thresholds for psychrophilic organisms, one of the reservoirs of useful genes. Sea mounts are facing increasing pressure by deep-sea fisheries, which is likely to result in high environmental impacts and extinctions (46). Little is known about the potential impacts of mining for sulfide deposits rich in gold and other metals located near hydrothermal vent ecosystems, but they are likely to be severe because these sites support the highest biomass concentrations in the deep sea (46). Other future threats include gas exploitation or mining near the summits of sea mounts, ridges, and other areas where sediment does not accumulate. Their distribution often coincides with hot spots of deep marine biodiversity, which are also located on hard substrates, away from the typical deep sea soft sediment (46). Finally, projects of massive CO₂ sequestration in the sea floor, with pilot studies already ongoing, also raise concern as a potential threat to deep sea biodiversity (47).

As agreed at the World Summit on Sustainable Development in Johannesburg, a global network of MPAs should be effective by 2012. There are ongoing efforts to reach an international consensus on the scientific criteria and guidelines underpinning this network. Also, the Conference of Parties to the Convention on Biological Diversity (CBD) (48) has recently made a significant step toward achieving this goal by adopting scientific criteria for identifying ecologically or biologically significant marine areas in need of protection and designing representative networks of MPAs (49). These criteria are well suited for the protection of MGRs because they target, among other things, the protection of rare, vulnerable, natural, or extreme environments and diversity hotspots. MPAs with general conservation goals are suitable for the preservation of MGRs because they target both known and yet to be discovered species. However, there is a perception of an inherent trade-off between conservation and other goals, such as fisheries management, which must be addressed (6). Although no single MPA design is likely to provide the perfect conditions for the preservation of all species, the emerging evidence indicates that carefully designed MPA networks are probably the best tool to meet both fishery and conservation goals (6). Although the scientific aspects involved in expanding and networking marine reserves are moving forward, the economic and governance structures required for the global protection of marine biodiversity remain ill-defined.

At the present state, MPAs encompass an area 10-fold lower than that of terrestrial protected areas (4), with most of these areas located within economic exclusive zones (EEZs) under national jurisdictions. However, 65% of the ocean lies beyond the EEZs, including many of the potential hot spots for MGRs, such as sea mounts and hydrothermal vents, which are mainly distributed in areas beyond national jurisdiction, thereby lacking a global governance framework to ensure their protection. Regarding the international waters outside the EEZs, the first article of the United Nations Convention on the Law of the Sea (UNCLOS) (50) defines the “area” as “the seabed and ocean floor and subsoil thereof, beyond the limits of national jurisdiction,” thereby clearly distinguishing it from the water

column referred to as “high seas” in the areas beyond national jurisdiction. Freedom of the high seas is warranted under conditions of part VII of the Convention. Cooperation is also promoted for the conservation of living resources, research, and resource exploitation in the high seas, with governments being responsible for activities of ships carrying their country flag. Although many MGRs are extracted from benthic organisms, part XI of the UNCLOS dedicated to the area is clearly restricted to the exploitation of mineral resources, under the management of the International Seabed Authority. The conservation of MGRs in the area can only be addressed by the International Seabed Authority under the framework of mineral exploitation, which will therefore manage limited and scattered protection zones in the area beyond national jurisdiction, such as the one being implemented for nodule mining in the Clarion–Clipperton zone (51).

On a more global scale, the General Assembly established a United Nations “Open-Ended Informal Consultative Process on Oceans and the Law of the Sea,” with an “Ad-Hoc Open-Ended Informal Working Group” to study issues relating to the conservation and sustainable use of marine biological diversity and genetic resources beyond areas of national jurisdiction (52, 53). Despite the establishment of regional fisheries management organizations, about two-thirds of fish stocks are either depleted or overexploited (54); therefore, there is a growing need to establish high seas MPAs for the protection of fisheries resources (55) that converges with the need for protection of general biodiversity, including MGRs. In addition, the implementation of high seas MPAs covering the water column, the sea floor, or both, and targeting specific environments, such as sea mounts and hydrothermal vents, will benefit the protection of MGRs in areas beyond national jurisdictions. Additional regulations, such as the requirement for environmental impact assessment of bioprospecting activities, would be desirable in some cases, particularly when large biomass collections or harsh techniques like trawling are required. However, enforcing a compulsory environmental impact assessment would require an international agreement on access and ownership of MGRs in areas beyond national jurisdictions, which is currently lacking.

Bioprospecting technologies are vulnerable to biopiracy practices, wherein individuals or corporations from technologically advanced countries may secure the intellectual property of resources derived from unique ecosystems in developing countries lacking the financial and technological resources to compete in this race. Thus, MPAs may help to reduce biopiracy by implementing clear policies regarding the use and sharing of the benefits generated by the resources they protect. Within national EEZs, biopiracy can be addressed by specific policies on genetic resources clearly defining the conditions for bioprospecting and access and benefit sharing. More explicit and robust national laws may also add to the ongoing efforts of the CBD toward an international regime on access and benefit sharing that should at least apply to EEZs (56). These access and benefit sharing policies should also accommodate other needs for access, such as basic academic research. Increasingly difficult access procedures have been reported to deter basic scientific research in the terrestrial environment (57) and could also condition basic marine research, biasing sampling efforts toward sites beyond national jurisdictions. Limitations to basic research on biodiversity could be detrimental, impeding the collection of the data that are needed for the implementation of the protection goals set by the CBD (57), particularly in developing countries. This situation could be eased by ensuring the transfer of knowledge and development tools necessary to build the capacity to conduct research on biodiversity in developing countries. Fear of biopiracy could also be alleviated by a clear mandate to disclose the origin of patented biological resources, a requirement that does not exist at present. Detailed information about the geographical and phylogenetic origins of MGRs would help states to settle disputes over intellectual property rights after a patent claim is made. Whereas the issue of biopiracy has been addressed by the CBD, this convention

applies strictly to the resources from EEZs, excluding the area and the high seas, which are by far the largest marine spaces to be explored and exploited, and where very profitable genes have already been isolated (58). The unregulated exploitation of MGRs in the absence of a universally accepted legal framework for the protection and equitable exploitation of the genetic resources of 65% of the ocean represents a 21st century technologically sophisticated version of the “tragedy of the commons,” affecting fisheries in international ocean waters (59).

In summary, the data reported here portray the appropriation of MGRs as a major recent development, with a huge prospect for scientific discovery and creation of wealth during the 21st century. The unfathomable biological diversity of the oceans offers a vast repertoire of potentially useful biological molecules with no comparable equivalent in terrestrial environments (60). Most importantly, whereas the use of marine organisms for food has often caused major ecological damage, the appropriation of their genetic resources is a potentially sustainable process but also requires conservation measures. Realization of the ample opportunities for science and business in the oceanic realm requires (i) halting the widespread loss of marine biodiversity, for which MPAs are key instruments, and (ii) the urgent development of international legislation regulating the conservation of these resources as well as access and benefit sharing for the vast economic and social benefits still to emerge. More specifically, high and deep seas MPAs must be created and international laws explicitly regulating the use and protection of biological resources beyond EEZs must be urgently agreed on for the effective protection of the vast pool of marine biodiversity and MGRs yet to be discovered in the in the high seas and the area.

Acknowledgments

We thank Sara Teixeira for technical help and Joël Querrelou and Elie Jarmache for useful discussions. This is a contribution to the MALASPINA 2010 project, funded by the CONSOLIDER-Ingenio 2010 program of the Spanish Ministry of Science and Technology (Reference CSD2008-00077).

References

1. Johannes RE (1978) Traditional marine conservation methods in Oceania and their demise. *Annu Rev Ecol Syst* 9:349–364.
2. Beverton R, Holt S (1957) *On the Dynamics of Exploited Fish Populations* (Chapman & Hall, London).
3. Committee on the Evaluation, Design, and Monitoring of Marine Reserves and Protected Areas in the United States, Ocean Studies Board, National Research Council (2001) *Marine Protected Areas: Tools for Sustaining Ocean Ecosystems* (National Academy Press, Washington, DC).
4. United Nations Environment Programme (UNEP) and International Union for Conservation of Nature (IUCN). World Database on Marine Protected Areas (WDPA). Available at <http://www.wdpa-marine.org/#/countries/> about. Accessed October 23, 2009.
5. Cragg GM, Newman DJ (2001) Natural product drug discovery in the next millennium. *Pharm Biol* 39:8–17.
6. Gaines SD, White C, Carr MH, Palumbi SR (2010) Marine Reserves Special Feature: Designing marine reserve networks for both conservation and fisheries management. *Proc Natl Acad Sci USA* 107:18286–18293.

7. Marra J (2005) When will we tame the oceans? *Nature* 436:175–176.
8. Benson DA, Karsch-Mizrachi I, Lipman DJ, Ostell J, Wheeler DL (2008) GenBank. *Nucleic Acids Res* 36 (Database issue):D25–D30.
9. Bouchet P (2006) The Exploration of Marine Diversity: Scientific and Technological Challenges (Fundación BBVA, Bilbao, Spain), pp 31–62 (in Spanish).
10. Hendriks IE, Duarte CM (2008) Allocation of effort and imbalances in biodiversity research. *J Exp Mar Biol Ecol* 360:15–20.
11. Corliss JB, et al. (1979) Submarine thermal springs on the galapagos rift. *Science* 203:1073–1083.
12. Kristensen R (1983) Loricifera, a new phylum with oschelminthes characters from the meiobenthos. *Z Zool Syst Evol* 21:163–180.
13. Chisholm SW, et al. (1988) A novel free-living prochlorophyte occurs at high cell concentrations in the oceanic euphotic zone. *Nature* 334:340–343.
14. Convention of Biological Diversity (2010) Census of Marine Life. Available at <http://www.coml.org/>. Accessed October 24, 2009.
15. WoRMS—World Register of Marine Species. Available at <http://marinespecies.org/>. Accessed October 24, 2009.
16. Blunt JW, et al. (2008) Marine natural products. *Nat Prod Rep* 25:35–94.
17. Dunkel M, Fullbeck M, Neumann S, Preissner R (2006) SuperNatural: A searchable database of available natural compounds. *Nucleic Acids Res* 34 (Database issue): D678–D683.
18. Trüper HG (1992) Prokaryotes: An overview with respect to biodiversity and environmental importance. *Biodivers Conserv* 1:227–236.
19. Duarte CM, Marbá N, Holmer M (2007) Ecology. Rapid domestication of marine species. *Science* 316:382–383.
20. Piel J (2004) Metabolites from symbiotic bacteria. *Nat Prod Rep* 21:519–538.
21. Thoms C, Schupp P (2005) Biotechnological potential of marine sponges and their associated bacteria as producers of new pharmaceuticals (part I). *J Int Biotechnol Law* 2:217–220.
22. Blunt JW, et al. (2009) Marine natural products. *Nat Prod Rep* 26:170–244.
23. Venugopal V (2008) *Marine Products for Healthcare: Functional and Bioactive Nutraceutical Compounds from the Ocean* (CRC Boca Raton FL), 1st Ed.
24. Bergé J, Barnathan G (2005) *Marine Biotechnology I* (Springer, Berlin), pp 49–125.
25. Mocz G (2007) Fluorescent proteins and their use in marine biosciences, biotechnology, and proteomics. *Mar Biotechnol (NY)* 9:305–328.
26. Adams MW, Perler FB, Kelly RM (1995) Extremozymes: Expanding the limits of biocatalysis. *Biotechnology (NY)* 13:662–668.
27. Cavicchioli R, Siddiqui KS, Andrews D, Sowers KR (2002) Low-temperature extremophiles and their applications. *Curr Opin Biotechnol* 13:253–261.
28. Hunt B, Vincent ACJ (2006) Scale and sustainability of marine bioprospecting for pharmaceuticals. *Ambio* 35: 57–64.
29. Proksch P, Edrada-Ebel RA, Ebel R (2003) Drugs from the sea—opportunities and obstacles. *Mar Drugs* 1:5–17.
30. Pomponi SA (1999) The bioprocess-technological potential of the sea. *J Biotechnol* 70:5–13.
31. Mendola D (2003) Aquaculture of three phyla of marine invertebrates to yield bioactive metabolites: Process developments and economics. *Biomol Eng* 20: 441–458.
32. Goffredo S, Lasker HR (2008) An adaptive management approach to an octocoral fishery based on the Beverton-Holt model. *Coral Reefs* 27:751–761.
33. Newberger NC, Ranzer LK, Boehnlein JM, Kerr RG (2006) Induction of terpene biosynthesis in dinoflagellate symbionts of Caribbean gorgonians. *Phytochemistry* 67: 2133–2139.

34. Towle MJ, et al. (2001) In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. *Cancer Res* 61:1013–1021.
35. Venter JC, et al. (2004) Environmental genome shotgun sequencing of the Sargasso Sea. *Science* 304:66–74.
36. Yooshep S, et al. (2007) The Sorcerer II Global Ocean Sampling expedition: Expanding the universe of protein families. *PLoS Biol* 5:e16.
37. Sogin ML, et al. (2006) Microbial diversity in the deep sea and the underexplored “rare biosphere.”. *Proc Natl Acad Sci USA* 103:12115–12120.
38. International Union for Conservation of Nature (2010) IUCN Red List of Threatened Species. Available at <http://www.iucnredlist.org/>. Accessed October 25, 2009.
39. Polodoro B, et al. (2008) Status of the World’s Marine Species (IUCN, Gland, Switzerland).
40. Staley JT (1997) Biodiversity: Are microbial species threatened? *Curr Opin Biotechnol* 8:340–345.
41. Weinbauer MG, Rassoulzadegan F (2007) Extinction of microbes: Evidence and potential consequences. *Endanger Species Res* 3:205–215.
42. Jackson JBC (2008) Colloquium paper: Ecological extinction and evolution in the brave new ocean. *Proc Natl Acad Sci USA* 105 (Suppl 1):11458–11465.
43. Carpenter KE, et al. (2008) One-third of reef-building corals face elevated extinction risk from climate change and local impacts. *Science* 321:560–563.
44. Intergovernmental Panel on Climate Change (2007) Climate Change 2007, the IPCC Fourth Assessment Report. Available at http://www.ipcc.ch/publications_and_data/publications_and_data.htm
45. ACIA (2004) Impacts of a Warming Arctic (Cambridge Univ Press, Cambridge, UK).
46. Glover AG, Smith CR (2003) The deep-seafloor ecosystem: Current status and prospects of anthropogenic change by the year 2025. *Environ Conserv* 30:219–241.
47. Metz B, Davidson O, de Coninck HC, Loos M, Meyer LA (2005) IPCC Special Report on Carbon Dioxide Capture and Storage: Prepared by Working Group III of the Intergovernmental Panel on Climate Change (Cambridge Univ Press, Cambridge, U.K.).
48. Convention of Biological Diversity (1993) Convention on Biological Diversity. Available at: <http://www.cbd.int/convention/convention.shtml> . Accessed March 24, 2009.
49. Convention of Biological Diversity (2007) CBD-EBSAs: Ecologically and Biologically Significant Areas. Available at <http://www.cbd.int/doc/meetings/mar/ewbcsima-01/information/ewbcsima-01-ewsebm-01-02-en.pdf> . Accessed October 26, 2009.
50. United Nations (1982) Convention on the Law of the Sea. Available at: http://www.un.org/Depts/los/convention_agreements/texts/unclos/unclos_e.pdf.
51. Smith CR, et al. (2007) Preservation Reference Areas for Nodule Mining in the Clarion-Clipperton Zone: Rationale and Recommendations to the International Seabed Authority. Workshop to Design Marine Protected Areas for Seamounts and the Abyssal Nodule Province in Pacific High Seas (University of Hawaii, Manoa, HI).
52. Zewers KE (2007) Bright future for marine genetic resources, bleak future for settlement of ownership rights: Reflections on the United Nations law of the sea consultative process on marine genetic resources. *Loy U Chi Intl L Rev* 5:151–176.
53. United Nations (2009) United Nations Open-Ended Informal Consultative Process Accessed October 28, 2009 Available at http://www.un.org/Depts/los/consultative_process/consultative_process.htm.
54. Cullis-Suzuki S, Pauly D (2010) Failing the high seas: A global evaluation of regional fisheries management organizations. *Mar Policy* 34:1036–1042.
55. United Nations Environment Programme-World Conservation Monitoring Centre (2008) National and regional networks of marine protected areas: A review of progress. Available at: <http://www.unep-wcmc.org/marine/pdf/MPA%20report%20FINAL.pdf>.

56. Convention on Biological Diversity (2010) Negotiations of the International Regime on ABS. Accessed June 14, 2010. Available at <http://www.cbd.int/abs/ir/>.
57. Martinez SI, Biber-Klemm S (2010) Scientists—Take action for access to biodiversity. *Curr Opin Environ Sustain* 2:27–33.
58. Vierros M, Hamon G, Leary D, Arico S, Monagle C (2007) An Update on Marine Genetic Resources: Scientific Research, Commercial Uses and a Database on Marine Bioprospecting (United Nations, New York) Accessed August 25, 2008. Available at http://www.ias.unu.edu/resource_centre/Marine%20Genetic%20Resources%20UNU-IAS%20Report.pdf.
59. Dietz T, Ostrom E, Stern PC (2003) The struggle to govern the commons. *Science* 302:1907–1912.
60. Newman DJ, Cragg GM (2004) Marine natural products and related compounds in clinical and advanced preclinical trials. *J Nat Prod* 67:1216–1238.
61. Euzèby J. (2009) List of prokaryotic names with standing in nomenclature. Available at <http://www.bacterio.cict.fr/number.html> . Accessed October 29, 2009.

Figures

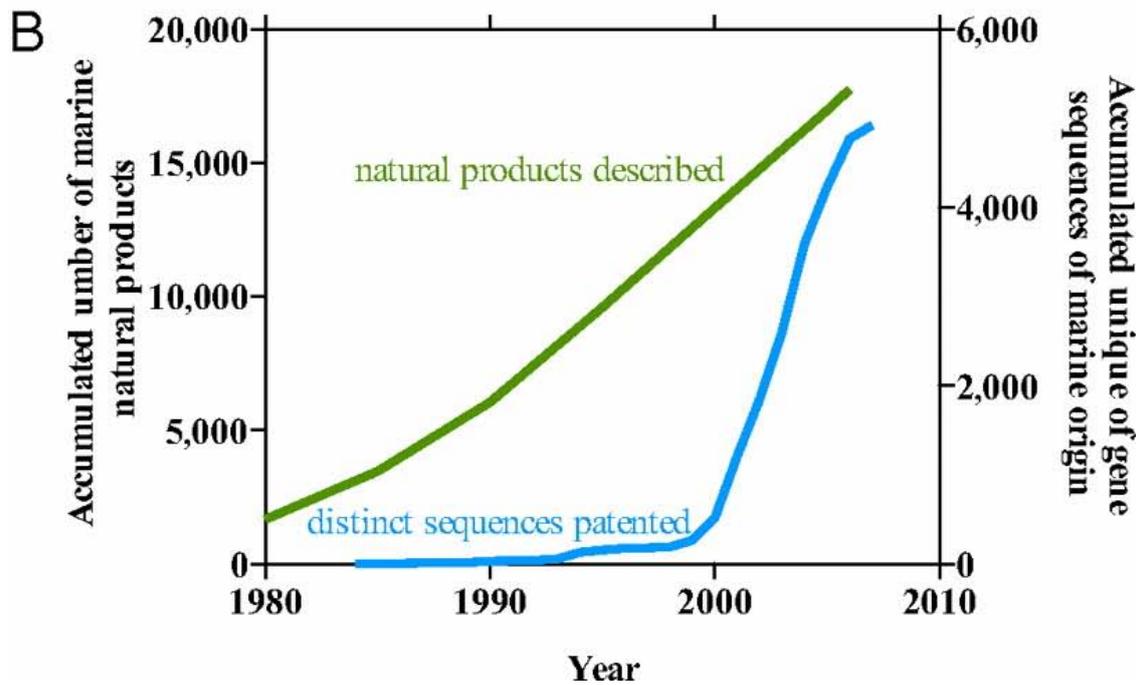
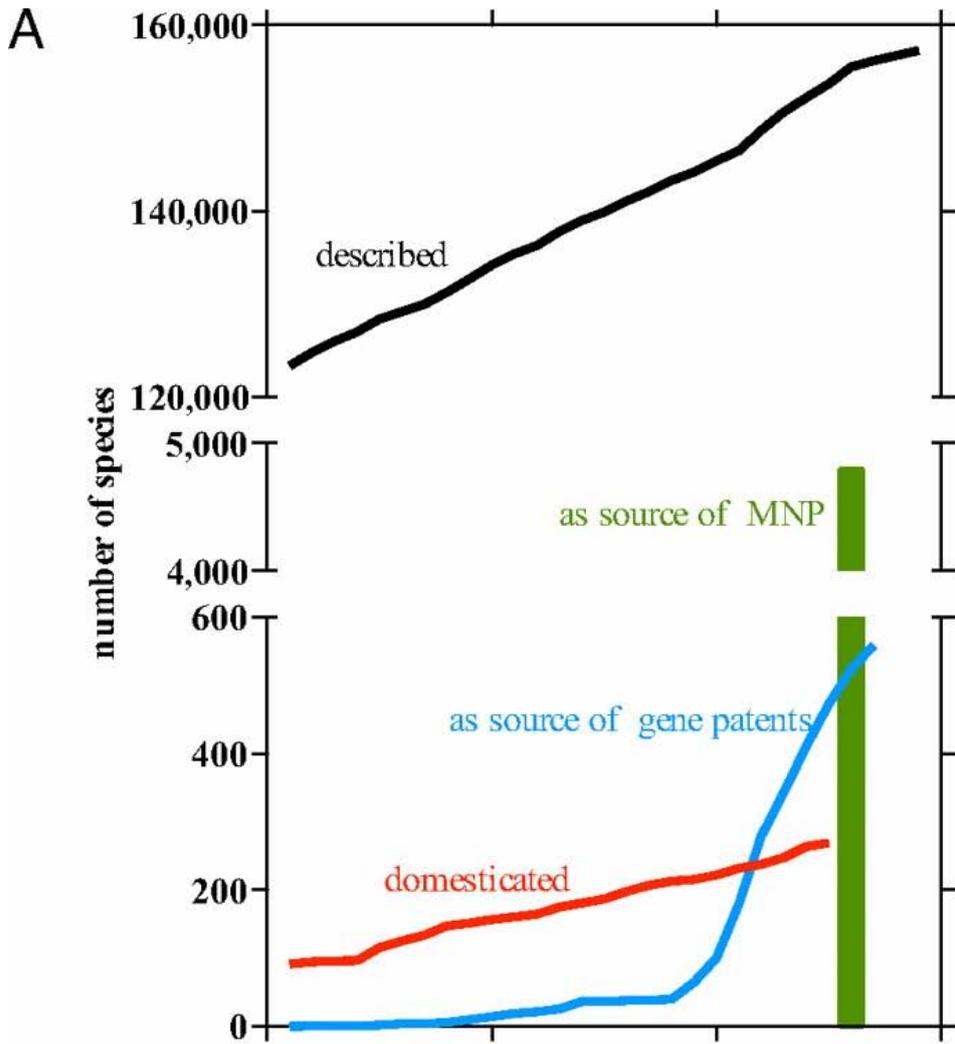


Fig. 1.

(A) Time course of the accumulated number of marine species described (black line), those domesticated for food (red line), those having sequences associated with patents in GenBank (blue line), and the total number of species reported as sources of natural products in the marine realm by 2006 (green column). Note the broken scale along the y axis. (B) Accumulated number of distinct natural products (green line) and sequences associated with patents reported in GenBank (blue line) over time.

Number of described marine species

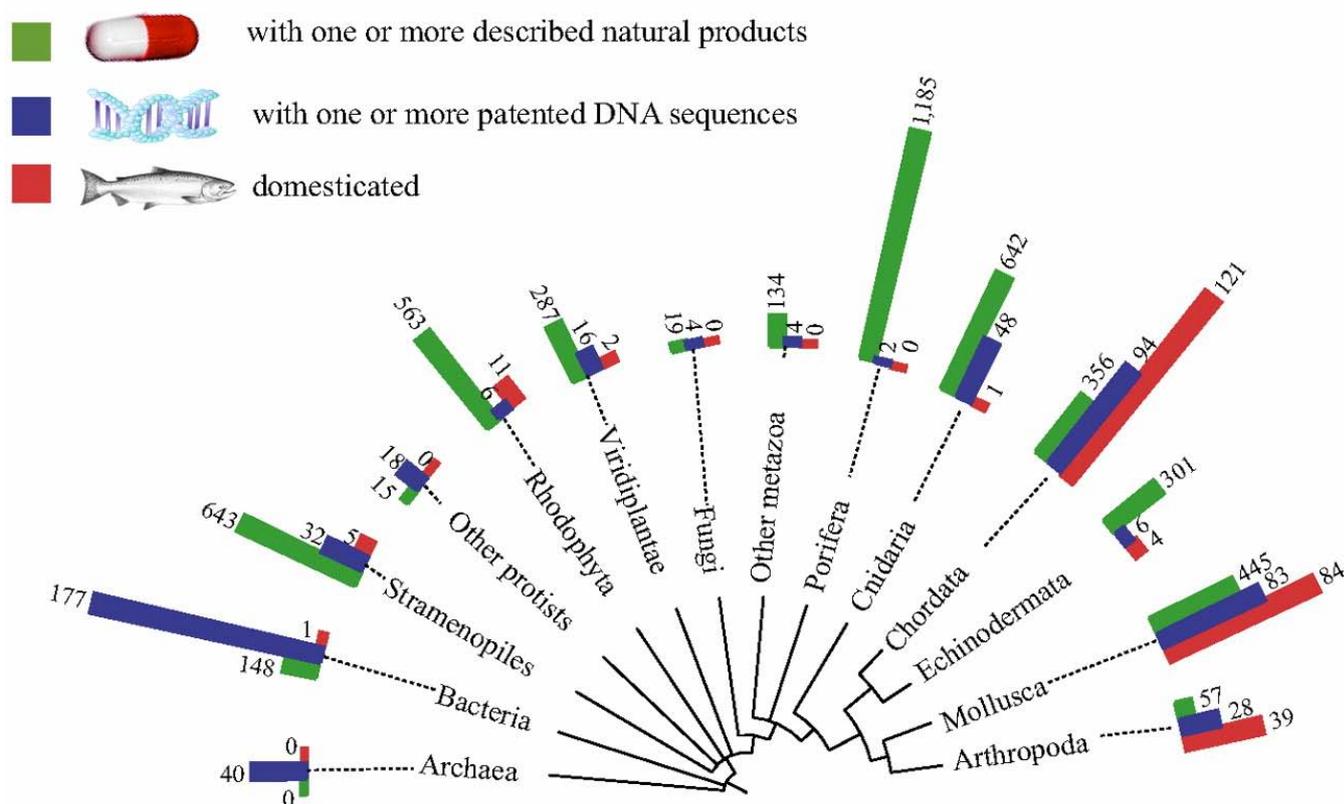


Fig. 2.

Phylogenetic affiliation of marine species as sources of DNA sequences in patents, natural products, and domesticated for food. Bar lengths correspond to the percentage of species in each taxonomic group relative to the total number of species for that particular use (natural products, sequences, or domesticated). The numbers show the actual number of species.

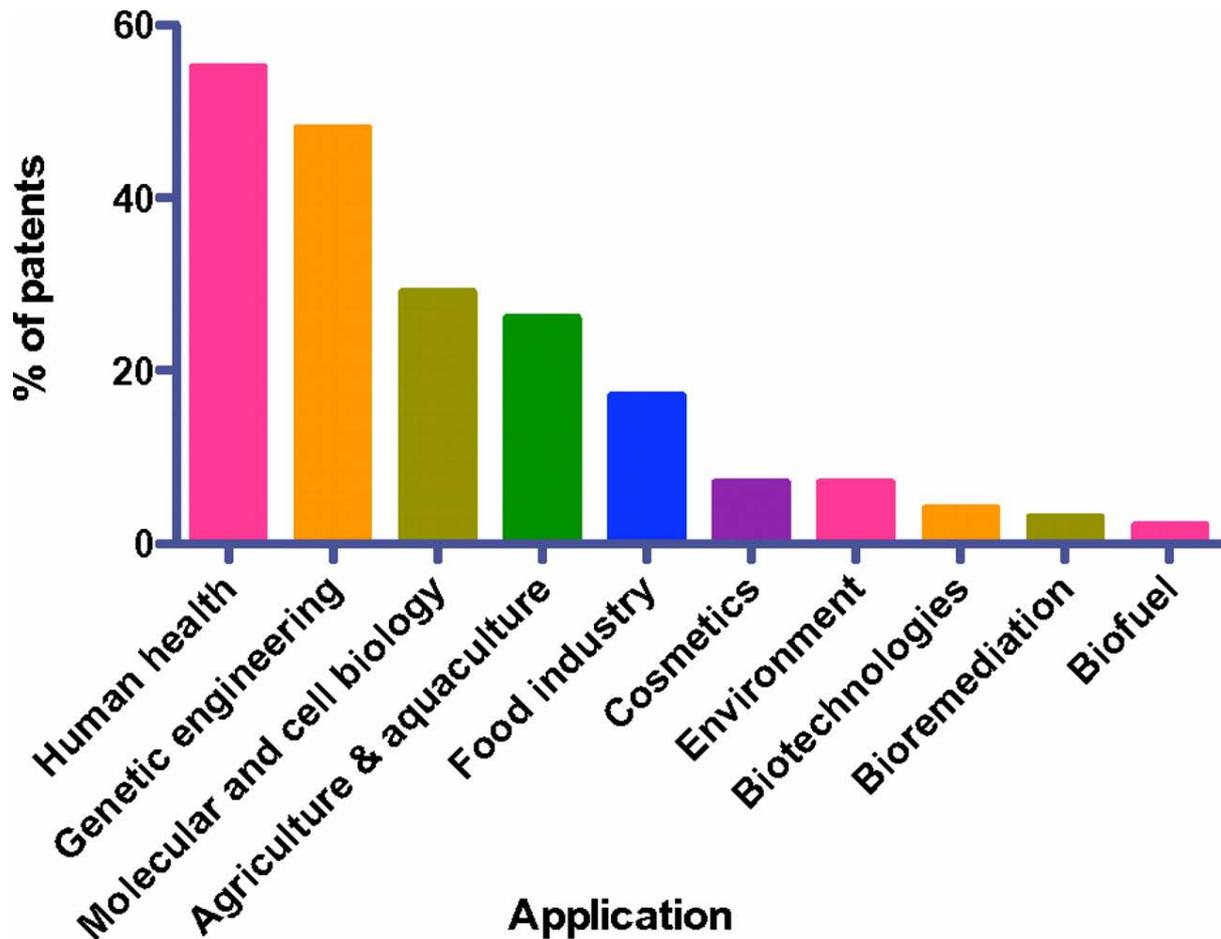


Fig. 3. Synthesis of the uses proposed in the claims or description of 460 patents deposited at the International Patent Office and associated with genes isolated in marine organisms. Because each patent claim can belong to several categories, the sum is larger than 100%.

Supporting Information

5. Methods

Data sources and processing

Data on patented DNA sequences were obtained from GenBank (1). The patent (PAT) division of GenBank release 165 (April 2008) contains 5,338,849 sequence records divided into 38 files, which were downloaded from the National Center for Biotechnology Information's Web site (<ftp://ftp.ncbi.nih.gov/genbank/>). Patent information was extracted and imported into a MySQL database (2) using Perl (3) scripts written for this purpose. The PAT division of GenBank contains patent records obtained from several patent authorities around the world, mainly from US, European, Japanese, and World patent organizations. Because the same sequences are often patented under different patent authorities, preliminary

analysis of the database revealed a large degree of redundancy in the reported sequences. Therefore, identical sequences reported under different patent authorities were detected and assigned a unique sequence serial number using Perl scripts to eliminate redundancy in the database.

Preliminary analysis of the taxonomic information included in the database revealed that 24% (1,329,921 sequences) of the reported patented sequences were synthetic constructs. Also, a large percentage of the sequences (37%) were tagged as unknown or unclassified, meaning that no taxonomic information was available. Sequences of unknown origin accounted for minor parts of the sequences reported by the European (<12% of reported sequences), Japanese (<17% of reported sequences), or World (<3% of reported sequences) patent organizations. None of the sequences linked to the US Patent Office contained any taxonomic information about their origin. However, about 60% of these unknown sequences belonging to the US Patent Office also appeared in the other patent databases. There may be some additional sequences originating from marine organisms, and even some additional marine species among these patented sequences of unreported origin that cannot be identified. Moreover, the information contained in the PAT division of GenBank is by no means exhaustive; therefore, it is likely that additional marine sequences have been reported under other patent authorities not covered here. Thus, the impressive number of marine species having patented genes reported in this study represents only a minimum estimate of the actual bioprospecting activity in the oceans.

The list of named species in the database was extracted, and the resulting name list was sorted and cleaned up manually to eliminate obvious spelling variants, typos, strain names or numbers, and other confounding information that could result in an overestimation of the number of named species. The list of clean unique species names was manually reviewed; marine organisms were identified and tagged in the database for subsequent analysis.

Information on the number of previously undescribed marine natural products reported per year and the corresponding phylogenetic information about the sources were compiled from several annual reports (4–9).

Because the taxonomic scheme used by GenBank (1) differs from that reported for natural products (4), the phylogenetic groups in Table S1 and in the trees in Fig. 2 and Fig. S1 have been chosen to match these two datasets and allow comparisons. Therefore, the chosen taxonomic affiliations do not represent a particular level (i.e., class, order) in a systematic hierarchy. The trees in figures 2 and fig S1 have been produced using the Interactive Tree of Life iTOL tool (10).

References

1. Benson DA, Karsch-Mizrachi I, Lipman DJ, Ostell J, Wheeler DL (2008) GenBank. *Nucl Acids Res* 36:D25–D30.
2. MySQL 5.1. Available at <http://dev.mysql.com/downloads>.
3. Perl 5.8. Available at <http://www.perl.org>.
4. Blunt JW, et al. (2008) Marine natural products. *Nat Prod Rep* 25:35–94.
5. Blunt JW, et al. (2007) Marine natural products. *Nat Prod Rep* 24:31–86.
6. Blunt JW, Copp BR, Munro MHG, Northcote PT, Prinsep MR (2006) Marine natural products. *Nat Prod Rep* 23:26–78.
7. Blunt JW, Copp BR, Munro MHG, Northcote PT, Prinsep MR (2005) Marine natural products. *Nat Prod Rep* 22:15–61.
8. Blunt JW, Copp BR, Munro MH, Northcote PT, Prinsep MR (2004) Marine natural products. *Nat Prod Rep* 21:1–49.
9. Blunt JW, Copp BR, Munro MH, Northcote PT, Prinsep MR (2003) Marine natural products. *Nat Prod Rep* 20:1–48.
10. Letunic I, Bork P (2007) Interactive Tree Of Life (iTOL): An online tool for phylogenetic tree display and annotation. *Bioinformatics* 23:127–128.

Tables

Table S1. Number of named marine species accounted as sources of patented genes, natural products, or domesticated for human consumption according to their taxonomic affiliation

Supporting Table 1

Taxonomic Group	Marine GenBank patents		Marine natural products		Domesticated species ***
	species*	sequences*	species**	compounds**	
Unidentified_Archaea	0	18	0	0	0
Crenarchaeota	13	124	0	0	0
Euryarchaeota	27	422	0	0	0
Cyanobacteria	14	92	118	602	1
Proteobacteria	103	739	29	3	0
Firmicutes	22	240	0	0	0
Bacteroidetes	17	52	1	4	0
Thermotogales	3	161	0	0	0
Dehalococcoidetes	2	109	0	0	0
Other_bacteria	16	62	0	0	0
Alveolata	11	28	0	0	0
Fungi	4	48	19	48	0
Haptophyceae	3	17	0	0	0
Euamoebida	1	3	0	0	0
Annelida	2	40	40	49	0
Arthropoda	28	124	57	23	39
Chordata	94	927	356	977	121
Cnidaria	48	498	642	3469	1
Ctenophora	2	3	0	0	0
Echinodermata	6	17	301	1074	4
Mollusca	83	760	445	1179	84
Porifera	2	16	1185	6668	0
Rhodophyta	6	20	563	1548	11
Chlorophyta	6	45	287	315	2
Streptophyta	10	135	0	0	0
stramenopiles	32	223	643	1476	5
Cryptomonadaceae	2	3	0	0	0
Euglenozoa	1	6	15	36	0
Bryozoa	0	0	63	180	0
Hemichordata	0	0	17	26	0
Nematoda	0	0	7	2	0
Platyhelminthes	0	0	7	33	0
Total	558	4932	4795	17712	268

*Unique sequences or named species (this paper)

** Data from (S4)

*** Data from (S10)

The number of unique sequences or natural products described for each taxonomic group is also reported. *Patented genes. Unique sequences or named species (this paper).

**Natural products. Data from Blunt JW, et al. (2008) Marine natural products. Nat Prod Rep 25:35–94.

***Domesticated for human consumption. Data from Duarte CM, Marbá N, Holmer M (2007) Ecology. Rapid domestication of marine species. Science 316:382–383

Supporting figure 1

Figure S1. Number of marine species subjected to different uses divided among different taxonomic groups.

