Chapter 29. Use of Marine Genetic Resources

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1. Introduction

The natural environment has long been a source of inspiration for new drugs and other products of biotechnology. Until relatively recently, the terrestrial environment, in particular, has been the primary source of genetic material and natural products at the centre of major new developments in biotechnology, including new drugs. Examples of natural products used in drug development include the anti-malarial drug quinine isolated from the bark of the *Chinchona*, the analgesics codeine and morphine from *Papaver somnifetum* latex, and antibiotics such as penicillins and tertracyclines from strains of *Penicillium* sp. and *Streptomyces* sp. The terrestrial environment contains far more known species of plants and animals than are at present known in the oceans (Hendricks et al., 2006; Mora et al. 2011), and has contributed greatly to the development of new biotechnologies, and new drugs in particular (Molinski et al., 2009; Arrieta et al., 2010; Leal et al., 2012). Yet there are many reasons to expect that the marine environment should represent a rich reservoir of novel genetic material and natural products, particularly those derived from animals and their microbiomes. Covering more than 70 per cent of the planet, and constituting 95 per cent of the volume of the biosphere, the oceans are home to a greater diversity of major animal groups (phyla) than the terrestrial environment (34 of 36 known phyla are found in the oceans *versus* 17 found on land). Most marine organisms have a large dispersal potential, either through the movement of adults, or through the dispersal of larvae by ocean circulation, potentially crossing hundreds to thousands of kilometres during their development. It is thus likely for many species that the same genomic background could be sampled both within several exclusive economic zones (EEZs) and in areas beyond national jurisdiction (ABNJ).

The study and utilization of marine genetic resources is a fairly recent human activity and, compared to the terrestrial environment, examples are relatively few and scattered throughout the world ocean. This chapter will therefore provide a general review of marine genetic resources (MGRs) rather than providing a regionally comprehensive and inclusive assessment. We will use a fairly broad definition of marine genetic resources that includes nucleic acid sequences, chemical compounds produced by marine organisms and unrefined materials extracted from marine biomass. Within areas under national jurisdiction, where marine organisms are most abundant and most accessible to researchers, MGRs and marine biodiversity are best known. MGRs in the vast, offshore oceanic areas beyond national jurisdiction (ABNJ) are, by comparison, poorly documented. The growing appreciation of the diversity and novelty of life in the oceans that has emerged from the results of programs such as the Census of Marine Life, and MicroB3 (Marine Microbial Biodiversity, Bioinformatics and Biotechnology - a European Union 7th Framework Program), have fuelled interest in the commercial possibilities of MGRs. Currently MGRs are important to the economies and sustainability of many sectors including the pharmaceutical industry (new medicines), cosmetics, the emerging nutraceutical industry, and aquaculture (new high-value high nutrition, healthy foods), biomedicine and many other economically and culturally important sectors.

Molinski et al. (2009) noted a decline since the mid-1990s in the interest of large pharmaceutical companies in the development of ‘drugs from the sea’. This is likely related to a general decline in all natural product research (Dias et al. 2012; Lahlou, 2012). Some hints of a recent resurgence exist, but it will be several years before it can be determined if this is a sustainable trend. In parallel with large commercial pharmaceutical interests reducing their activity in this sector, activity increased in smaller academic-industry partnerships in developed countries, resulting in the emergence of small-scale, start-up companies. New and affordable developments in analytical technologies (gene sequencing, biomolecule characterization) have helped drive this new trend. Further evidence of increased interest in MGR is found in an analysis by Arrieta et al. (2010), who noted growth over the past decade in the accumulation of patent claims related to marine organism genes (currently increasing by 12 per cent per year) and identified marine natural products. In the context of its work on the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction (ABNJ), the United Nations General Assembly stressed the need for a comprehensive regime to better address the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction. Marine genetic resources, including questions on the sharing benefits, are part of the package of issues to be addressed by the preparatory committee established to make substantive recommendations to the Assembly on the elements of a draft text of an international legally-binding instrument under the United Nations Convention on the Law of the Sea (resolution 69/292).

2. Marine Pharmaceuticals

Marine biodiversity in theory has enormous biotechnological potential. Yet, to date, despite “repeated waves of enthusiasm and much early promise,” examples of successful development of commercial products are very few. In the early 1950s, the first marine bioactive compounds, spongouridine and spongothymidine, were isolated from the Caribbean sponge *Cryptotheca crypta*. The 1970s saw the beginning of basic scientific research in chemistry and pharmacology of marine natural products and directed efforts in drug development (Molinski et al., 2009; Mayer et al., 2010).

However, only in the last decade have these research efforts resulted in the production of a first generation of drugs from the sea into clinical trials. Not until 2004 was the first drug from the sea (developed from a neurotoxin produced by a tropical marine cone snail, *Conus magnus*) finally approved for sale on the market under the name Prialt; it is used in the treatment of chronic pain associated with spinal cord injuries. More recently, in 2007, a second drug, the anti-tumour compound trabectedin (known as Yondelis, discovered from the colonial tunicate *Ecteinascidia turbinata*), was approved for the treatment of soft-tissue sarcoma in the European Union. Seven drugs derived from marine organisms are currently approved by the United States Food and Drug Administration (FDA) and on the market (Mayer et al., 2010; http://marinepharmacology.midwestern.edu/clinPipeline.htm). An example of a medical but non-pharmaceutical usage of compounds produced by marine organisms are wound treatment ‘dressings’ made of marine diatom polymers (Marine Polymer Technologies Inc.).

3. Marine Nutraceuticals

Related to the biopharma industry, attention also increasingly focuses on so-called marine nutraceuticals. These compounds (or ‘substances’) are found to be beneficial to human health and “delivered” via food or food products (Kim, 2013). Commercial efforts are also underway to synthetically produce some of these substances. Compounds of interest comprise a wide variety, including polysaccharides, polyphenols, bioactive peptides, polyunsaturated fatty acids, and carotenoids; with identified anticancer, anti-inflammatory, anti-oxidant, and antimicrobial activities (Guerard et al., 2010; Ngo et al., 2011; Vidanarachchi et al., 2012). Many of the products derive from marine algae and include, for example, Fucoidan, a sulfonated polysaccharide found in brown algae and shown to benefit immune system and gastrointestinal health by neutralizing free radicals. Other examples are: Vitamin C and carotenoids, anti-oxidants obtained from *Chlorella* sp.; Spirulina (cyanobacteria of the genus *Arthrospira*), used as a natural blue food colorant and contains a wide variety of nutrients, such as B vitamins, minerals, proteins, linolenic acid, and anti-oxidants such as beta carotene and Vitamin E.

In contrast to the more limited development of new drugs from marine organisms, the nutraceutical industry in Europe and Asia is experiencing significant growth. Marine and algal omega-3 products alone accounted for 1.5 billion United States dollars in sales in 2009, and the global nutraceutical industry as a whole is estimated to grow to a 180 billion US dollars business by 2017 (Kim, 2013). This rapidly growing sector often uses marine biomass, such as fish waste or harvested algae, to produce health food products and restorative cosmetics.

4. Marine organism-derived anti-foulants and adhesives

The antifoulant and marine adhesives industries have a long history. The costs of biofouling to the fleets around the world are estimated to run into 100 million US dollars each year. Many biocidal antifoulants are now banned (e.g., copper-based paints) because of their direct toxicity to marine organisms. Tributyl tin-based products, once used extensively, are now banned because of their now well-known impact on sex determination in marine molluscs and other organisms. Naturally derived antifoulants include enzymes, antimicrobials, biomimetics such as novel topographies, and natural chemical signals (Callow and Callow, 2011; Kirschner and Brennan, 2012; Gittens et al., 2013)

Marine algae are an important source of novel antifouling compounds and mangroves and sponges also feature high on the list of exploited marine organisms. Many algal species produce compounds that inhibit growth of marine bacteria. A red algal metabolite has been shown to affect the composition and density of bacterial colonies, and compounds from the mangrove plant reduce larval barnacle settlement. Such identified active natural compounds inspire the commercial synthesis of mimetics that are more stable and easily applied to surfaces, such as ship hulls, docks etc. (Callow and Callow, 2011; Kirschner and Brennan, 2012; Gittens et al., 2013).

Although the antifoulant industry seeks to prevent undesirable attachments, the bio-adhesive industry focuses on marine glues, materials that enable stable and robust adhesion under water. Perhaps not surprisingly, target organisms used as potential sources of novel marine glues are precisely those that the antifoulant community seeks to deter, for example, barnacles, mussels, tube-building worms and echinoderms. All successfully attach to wet surfaces with tenacity and therefore provide a rich source of ideas for novel adhesives. Some (starfish) uniquely have strong yet temporary adhesives used to anchor their feet during locomotion (Kamino, 2010; Stewart et al., 2011; Petrone, 2013). The mechanisms employed often involve complex surface chemistries and physico-chemical three-dimensional properties, but nevertheless often have a simple biochemical basis. For example, one of the most widely employed core substances is L-Dopa, whilst extracellular DNA is also thought to be an important component in some bio-adhesives (Kamino, 2010; Stewart et al., 2011; Petrone, 2013). Bulk harvesting of natural glues from marine organisms is impractical and any economic exploitation will require an extensive research effort directed at the chemical structure and genetic basis of the natural glues produced by marine organisms.

5. Environmental, economic and social aspects of MGR research

Marine scientific research related to MGR involves the collection of ocean data and the collection of biological samples from the water column and the seabed. Most scientific instruments and sampling devices so far cause negligible harm to marine habitats. Nonetheless, in some parts of the seabed scientific sampling is concentrated in relatively small areas, such as at well-studied hydrothermal vent fields. There, competing uses have arisen between researchers requiring physical samples (biological or geological) and researchers wishing to observe the natural evolution of local ecosystems (Godet et al., 2011). Such use conflicts led to the adoption of codes of best practices by international organizations such as InterRidge (http://www.interridge.org/publications) (see Chapter 30 on Marine scientific research).

Although the possibility still exists of direct extraction of new natural products from marine biomass, such as the extraction of compounds from seaweeds and oils from Sargassum or krill, future exploitation of MGR for purposes of developing the genetic resource is unlikely to involve substantial large-scale harvesting of marine organisms and the resultant destruction of habitat and depletion of species populations as caused by fisheries. Indeed, if recent trends can be used as a guide, future MGR products will come from laboratories and larger facilities where genes and biomolecules will be discovered, and then incorporated into industrial processes that may involve the artificial synthesis of biomolecules (e.g. Mizuki et al., 2014; Wilde et al., 2012; Newman and Cragg, 2012), or the insertion of desired genes into microbes that then produce the desired molecule (Newman and Cragg, 2012). However, potential for habitat damage exists even from scientific fieldwork, particularly in vulnerable marine ecosystems and areas of intensive study and sample collection. In addition, the success of nutraceutical extraction from fish waste could lead to the large-scale harvesting of stocks with little or no food value to humans but attractive as sources of biomolecules for commercial products.

Benefits arising from MGR research include improved knowledge of marine biodiversity and the importance of biodiversity to the provision of ecosystem services and the maintenance of ocean health. Related marine natural products research will also result in more efficient, value-added exploitation of marine resources, as described above. Any accelerated growth in the MGR research sector will not only profit the marine pharmaceutical industry, but also result in health and other social benefits from access to the pharmaceutical or other products themselves (Leary and Juniper, 2014; Broggiato et al., 2014).

6. Capacity to engage in MGR research

6.1 Research Vessels

The first step in the process of accessing MGRs is the collection of samples in the field. In inter-tidal and coastal waters, the capacity to collect biological samples does not require advanced technology. Smaller vessels, even sailing vessels, can be used to sample water column organisms. For example, two recent expeditions used the privately owned sailing yachts; Tara (http://oceans.taraexpeditions.org/index-o.php/en) and Sorcerer II (www.jcvi.org/cms/research/projects/gos/overview/) to conduct ocean basin-scale surveys of planktonic microorganisms. Further offshore sampling of deep-water organisms and the seabed requires an offshore-capable ship (defined here as greater than 60 metres in length) and in most cases a specialized research vessel. Operating costs for these larger vessels are typically greater than 25 000 United States dollars per day. At first glance, basic capability to engage in MGRs research appears to be fairly widespread among nations. The International Research Vessel database (www.researchvessels.org) lists 271 vessels greater than 60 metres in length available in more than 40 countries. However, the majority of these vessels belong to a few developed countries, as shown in Figure 1 (Juniper, 2013).

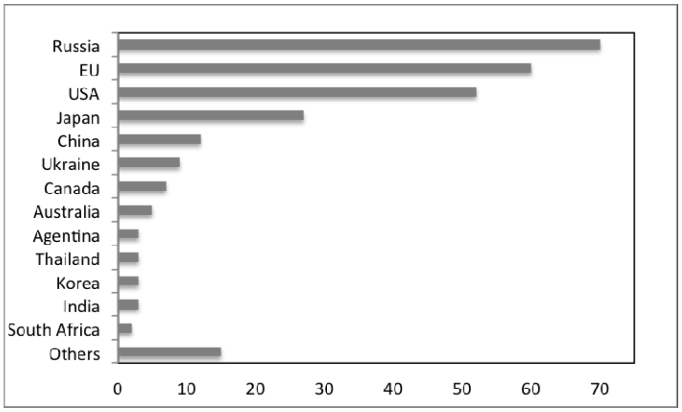


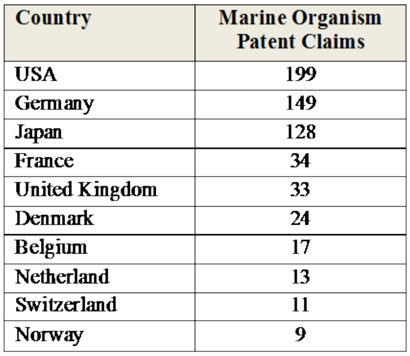
Figure 1. Geographic distribution of offshore research vessels (60 m or greater in length). Source: International Research Vessel Database.

At sea, most biological specimens are collected by lowering or towing sampling devices from the vessel (Juniper, 2013). Heavier gear, e.g., winches, cables, dredges and corers, is required to sample the seabed, where the majority of known marine species are found. This latter requirement reinforces the importance of larger, motorized research vessels for accessing biodiversity at depths of several kilometres. Some sampling devices are highly specialized and not all research vessels have the same collecting capacity. This is especially true for remotely operated vehicles (ROVs), which are used to locate and sample hydrothermal vent ecosystems, a source of novel species adapted to extreme conditions. Hydrothermal vent sites are very small in area, usually tens to hundreds of square meters, and cannot be easily sampled or even located by lowering standard sampling devices from ships. They require precisely navigated diving with ROVs or human-occupied submersibles, although the latter are used less frequently than ROVs. These vehicles are capable of diving to much deeper depths than military submarines, and are equipped with robotic arms, video cameras and various sampling devices. The list of States possessing and operating deep-diving scientific submersibles is limited to a subset of the developed countries currently leading marine scientific research efforts globally, such as the USA, Canada, the UK, France, the Russian Federation, Japan and most recently China, India and South Korea (Juniper, 2013). ROVs can also be chartered from commercial firms that provide support for the offshore petroleum industry, but most of these vehicles are limited to depths of less than 2,000 metres.

6.2 Biodiversity Expertise

Another important capacity related to accessing and deriving value from marine biodiversity is the specialist knowledge required to identify species, both known species and those new to science (Hendriks & Duarte, 2008; Juniper, 2013). Marine biodiversity specialists are mostly trained in developed countries with a long history of botanical and zoological scholarship in universities and museums. One way to measure the worldwide distribution of marine biodiversity expertise is to examine the level of publication activity in the scientific literature in relation to the country of affiliation of the lead author on these publications. A recent review of the literature revealed that the majority of publications in the field of marine biodiversity come from relatively few developed countries (Hendriks and Duarte, 2008).

Table 1. Geographic distribution of patent claims for genes of marine origin. Source: Arnaud-Haond et al. (2011).



Country	Marine Organism Patent Claims
USA	199
Germany	149
Japan	128
France	34
United Kingdom	33
Denmark	24
Belgium	17
Netherland	13
Switzerland	11
Norway	9

These specialists are experts in the morphological identification of specimens and, increasingly, the interpretation of DNA sequence information that is used to identify marine plants, animals and microbes. It could be argued that this scientific expertise is of greater importance to the usage and application of MGR than is access to laboratories that can produce gene sequence and biochemical composition information from field samples. Many countries have commercial sequencing and biochemical analysis facilities that serve national and international organizations/institutions, and academic and private clients. The raw data produced by these facilities require expert interpretation before they can be used to identify species, genes and biochemical compounds of interest. Table 1 illustrates the dominance by applicants from a few developed countries in recent patent claims associated with genes of marine origin according to a database undertaken by Arnaud-Haond *et al.* (2011). The top ten countries account for 90 per cent of filed gene patents, with 70 per cent from the top three (Arnaud-Haond et al. 2011). Relatively new approaches, such as microbial metagenomics, also require sophisticated bio-informatics tools and training and these are most accessible in developed countries. Nevertheless, some (growing?) capabilities in bio-informatics and genomics exist in developing countries, particularly in the health and agricultural science sectors, and these skills could be adapted and applied to the exploitation of MGRs.

6.3 Deriving Economic Value from MGR

Few examples exist of a direct developmental path from field collections of marine organisms through to the commercialization of marine natural products or genes from marine organisms. The Vent Polymerase enzyme is one example of a rapid transition from the discovery of a new microorganism in the field to the commercialization of a biomolecule (Mattila et al, 1991). Field research in the marine environment is primarily led by academic or government scientists and is aimed at increasing our knowledge of the ocean and the organisms that it supports. It is this knowledge base that may be later used by laboratory-based scientists in academia, industry and government in research more directly related to the eventual use of MGR for commercial purposes (Brock, 1997; Juniper, 2013). Surprisingly few direct connections are found between these basic and applied research sectors.

A review by the journal *Nature* (Macilwain, 1998) concluded that tens to hundreds of thousands of failed prospects exist for every example of a commercially successful natural product. One measure of success at extracting drugs from the sea is the number of drugs from marine organisms approved for commercialization by the FDA. Currently (June 2014) only seven drugs from marine organisms have received FDA approval (see also above), and approximately twice that number are in clinical trials (http://marinepharmacology.midwestern.edu/clinPipeline.htm). Mayer et al. (2010) note that the pre-clinical pipeline “continues to supply several hundred novel marine compounds every year and those continue to feed the clinical pipeline with potentially valuable compounds.”

Among the myriad marine life forms, the greatest unknown potential source of novel bioproducts is marine microorganisms (Gerwick et al., 2001). The advent and applications of genome, proteome, and transcriptome analyses are helping to recognize the enormous extent of marine microbial diversity and deepening our understanding of how the chemistry of the ocean and its interaction with the atmosphere are also mediated by microbial metabolism. From the bioprospecting perspective, the biomolecules produced by marine microbes remain virtually unstudied for potential commercial applications.

Microbial bioproducts will remain undeveloped unless there is a feasible alternative to mass culturing and efficient harvesting. In general, molecular approaches offer particularly promising alternatives, not only to the supply of known natural products (e.g., through the identification, isolation, cloning, and expression of genes involved in the production of the chemicals), but also to the discovery of novel sources of molecular diversity (e.g., through the identification of genes and biosynthetic pathways from uncultured microorganisms; Bull et al., 2000).

6.4 "Omics" Tools

Recent breakthroughs in marine metagenomics are paving the way for a new era of molecular marine research. Metagenomic studies of marine life are yielding new insights into ocean biodiversity and the functioning of marine ecosystems; for the first time we can explore ecological interrelationships at the gene level. The first study of this type, led by the J. Craig Venter Institute, used these tools to survey marine microbial diversity, discovering thousands of new species, millions of new genes and thousands of new protein families. A seminal 2004 paper described how the analysis of 200 litres of surface water from the Sargasso Sea enabled the identification of about 1,800 genomic microbial species and 1.2 million unknown genes using an environmental metagenomic shotgun approach (Venter et al., 2004). This work led to other marine metagenomic studies, such as those reviewed by Gilbert and Dupont (2011) that show how massive sequencing of environmental samples can lead to the discovery of extraordinary microbial biodiversity and to the unravelling of important components of the pathways of phosphorus, sulphur, and nitrogen cycling. These powerful molecular tools are enabling a new "study it all approach" to discovering organismal, genetic, biomolecular and metabolic diversity in the oceans at an accelerated pace, as exemplified by the recent round-the-world Tara expedition (Ainsworth, 2013) that returned over 25,000 samples of water column organisms for intensive molecular analysis with so-called 'omics' tools.

7. The importance of understanding life histories, plasticity and the impact of climate change

Climate change and ocean acidification are widely recognized as increasing threats to marine ecosystems impacting growth, survival, reproduction, and many other phenotypic features of all marine organisms, leading to changes in species abundances and distribution. Many key marine invertebrates, including crabs, echinoderms and molluscs often have equally if not more complex life histories with several, vulnerable, free-swimming planktonic stages before they metamorphose and settle to their adult benthic form. These sophisticated morphological and physiological processes are underpinned by complex gene regulatory networks and genomic pathways (Gilbert, 2013). This is significant because although it is now increasingly clear that predicted climate change events will affect marine biota, it is also now clear that several key organisms exhibit a valuable plasticity in the face of environmental stresses and challenges (Byrne and Przeslawski, 2013; Chan et al., 2015a, b; Dorey et al., 2013; Harley et al., 2006; Merila and Hendry, 2014; Reusch, 2014; Stumpp et al., 2011a, b; 2012; Thor and Dupont, 2015). Understanding and exploring this potential will be vital if we are to identify resilient and potentially phenotypically plastic populations. Identification of the genetic bases of this plasticity will be an important resource to the future of exploited marine species in a changing ocean.

8. Conclusion

The commercial utilization of MGRs had very modest beginnings in the 20th century, particularly when measured against the estimated potential of the great diversity of species and biomolecules in the sea. More promisingly, the past decade has seen the commercialization of the first drugs derived from marine organisms, and considerable growth in nutraceutical and other non-medical uses of marine natural products. This past decade has also seen an astounding increase in our capacity to discover novel marine organisms and biomolecules and understand the genomic basis of life in the oceans. New technologies are fostering a new wave of optimism about the commercial potential of MGRs that is influencing funding priorities for marine research and has led to the emergence of futuristic terms, such as ‘blue growth’ and the ‘knowledge-based blue economy of tomorrow’. Much of the capacity for discovery and commercialization of MGRs remains in the hands of a few developed countries. Much of the genetic diversity in our seas and oceans remains unknown and relatively unexplored; yet more potential is to be realized, particularly in the context of climate change. While this chapter has emphasized the commercial utilization of marine genetic resources, there are strong arguments to be made for the value to societies and ecosystems of simply protecting and conserving marine genetic resources (e.g. Pearce and Moran, 1994).

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Additional Reading

The European Marine Board (http://www.marineboard.eu/) has been responsible for generating policy advice, position papers, vision documents, etc., that review the importance of “blue biotechnology;” most are available as free downloads, for example “Marine Biotechnology: a Vision and Strategy for Europe” (http://www.marineboard.eu/publications/full-list). This is a review of the state of the art in marine biotechnology and its significant potential to contribute to scientific, societal and economic needs (2010). In addition, the European Commission has hosted several projects that summarize and highlight the needs and advantages of developing coordinated programmes for harnessing and sustainably exploiting products from our seas and oceans; often generically referred to as “Blue Growth,” it includes all aspects of marine and maritime technology (http://ec.europa.eu/maritimeaffairs/policy/blue_growth/index_en.htm).

Other organizations, for example the National Association of Marine Laboratories (NAML) (http://www.naml.org/) in North America also produce regular position papers from marine expert groups.