MARINE NATURAL PRODUCTS BIOTECHNOLOGY

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Contents

Summary

Marine natural products discovery is a complex multidisciplinary endeavor that includes the search for new pharmaceuticals, and the isolation and production of enzymes, dietary supplements, and biopolymers. Several promising compounds derived from marine sources are in clinical trials and show great potential for development as pharmaceuticals. These compounds include bryostatin-1 from a bryozoan, dehydrodidemnin B and ecteinascidin-743 from tunicates, ziconotide from a cone shell, and halichondrin B and discodermolide from sponges.

Marine microbes, including actinomycetes and fungi, have great potential as sources of novel bioactive compounds. As more compounds progress through clinical trials, an important issue is the need for large-scale production. In some cases, microbes associated with marine invertebrates may be the source of compounds of interest. If the producing microbe can be isolated, this may provide a sustainable source of the compound in fermentation systems. Aquaculture of marine invertebrates is likely to be important to obtain a reliable supply of some compounds. Collection of invertebrates from natural sources may have detrimental environmental consequences that must be considered but “bioprospecting” can also have beneficial environmental outcomes. Equitable benefit sharing with countries in which biodiverse material is collected is

important. Future developments in genomics and bioinformatics are likely to result in a proliferation of drug targets for screening. The need for novel extracts for screening will grow and this is likely to stimulate efforts to discover novel marine natural products.

1. Historical Development

There was a sense of optimism at the "Drugs from the Sea Conference" held in 1967 at the University of Rhode Island (US), during which marine natural products discovery was a key theme. It was envisioned at this conference that there would be rapid progress in the discovery and commercialization of new marine compounds. It is now clear that this optimism was misplaced, since it has taken more than three decades to progress to the point where several pharmaceutical compounds derived from marine sources are in the final stages of clinical trials.

There are several reasons for the slowness of this process compared with the discoveries of natural products from terrestrial sources. Collection of samples from the marine environment is inherently much more difficult and expensive than terrestrial sample collection. Pharmaceutical companies generally do not have the expertise in-house to access high-quality marine samples, and have not been prepared to make the investment in ships and personnel to mount effective marine expeditions. Companies have therefore needed to form partnerships with scientists at academic institutions and these interactions are sometimes awkward and inefficient since academic and commercial goals are often not entirely congruent.

Most collection efforts have been, and remain, limited to shallow coastal waters. Collection of the enormous biodiversity present in waters deeper than 30 m (and therefore out of easy reach of scuba divers) has relied on trawling in which organisms are often damaged. With this collection method, organisms are not seen in their natural environment and valuable information about potential interactions is therefore lost. For example, in the case of a sponge producing a compound that inhibits growth of competing organisms and as a result is surrounded by a clear area, this clue to its bioactivity would not be observed for a deepwater sponge collected by trawling. The ideal method for collection of deepwater samples is by use of manned research submersibles but there are only a handful of institutes worldwide that possess this capability.

Another important reason for the slow progress in marine natural products discovery is that microbiological investigations, especially those focused on fungi and actinomycetes, have lagged behind those in the terrestrial environment. Terrestrial fungi and actinomycetes have proven to be excellent sources of bioactive compounds. For example, two-thirds of all naturally-occurring antibiotics have been isolated from actinomycete bacteria (see *Production of antibiotics*). It is only in the past decade that many microbiologists have come to accept that there is an indigenous assemblage of actinomycetes in the marine environment. Now that marine fungi and actinomycetes have started to receive the attention that they deserve as potentially very important groups for natural products screening, rapid progress should be made in the identification and isolation of bioactive compounds from these microbes.

2. Present Development

2.1. Introduction and Scope

Marine natural products discovery and production is a complex, multidisciplinary endeavor. Discovery of a compound from a marine organism can require interaction between marine biologists, microbiologists, chemists, and pharmacologists. Many of the research activities involved in the discovery of novel compounds from the marine environment fall into the area of marine biotechnology, broadly defined as "the application of scientific and engineering principles to the processing of materials by marine biological agents to provide goods and services". Increasingly, molecular approaches are important in this process. Molecular taxonomy can be important in identifying the producing organism (microbe or macroorganism) and in "dereplicating" collections of organisms, for example, in identifying duplicate strains of bacteria in a culture collection. Molecular genetic techniques (see *Methods in genetic engineering*) have become indispensable during the last decade for identifying targets for drug screening. The screening process has evolved from whole-organism based screens to molecular screens in which the interaction of extracts and compounds with individual enzyme systems is determined as the basis for selection of compounds with important bioactivity. The next important frontier in the commercialization of marine natural products is to ensure a ready and inexpensive supply of compounds from marine sources for the pharmaceutical industry. In many cases, the compound of interest may be produced by symbiotic microbes rather than the invertebrates in which activities are first discovered. Molecular approaches, such as the use of gene probes, may be useful in location and identification of the "producer" microbe. If this microbe can be isolated and production of the bioactive compound maintained in fermentation systems, the problem of harvesting elusive and possibly endangered invertebrates from the marine environment can be circumvented.

The major effort in marine natural products discovery is focused on compounds of pharmaceutical interest. Marine microorganisms and macroorganisms are screened for production of bioactive compounds as part of the overall research effort in natural products discovery. This is one component of research and development for drug discovery, a process in which pharmaceutical companies invest over US$20 billion per annum. An increasing proportion of natural products research funding is being devoted to programs focused on the marine environment. Marine samples are attractive to pharmaceutical companies in order to reduce the problem of "re-discovery" of compounds from relatively well-characterized terrestrial sources and because of the realization that unique classes of molecular structures not found in terrestrial biota are present in the marine environment.

Marine natural compounds are not limited to compounds of pharmaceutical importance. Enzymes from marine organisms (see *Marine microbial enzymes*), in particular marine microbes, may have considerable commercial value. Also, "bulk" compounds from the marine environment, such as seaweed and seaweed products, can be included as natural products, the production of which may be enhanced by application of a biotechnological approach.

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http://clinicaltrials.gov/ [This site gives details on clinical trials of many of the compounds mentioned here.]

http://www.diversa.com/markprod/prod/pyro.asp [This web site describes the Pyrolase ™ enzymes marketed by Diversa Corporation.]

http://www.unep.ch/bio/conv–e.html [This web site gives the text of the Convention on Biological Diversity].

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Biographical Sketch

Russell T. Hill is a molecular microbial ecologist who investigates groups of marine bacteria that are important for natural products discovery. Current research interests include actinomycete bacteria from the marine environment and microbes associated with marine sponges. Dr. Hill is an Associate Professor at the Center of Marine Biotechnology, University of Maryland Biotechnology Institute where he heads an active research laboratory partly funded by collaborations with pharmaceutical companies.