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Marine Bioprocess Engineering: Building Bridges from Discovery to Commercialization of Marine Natural Products

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Abstract

Numerous novel marine natural products have been discovered and isolated from varied marine organisms by the diligent bio-prospectors over the past decades. An assessment of the current status of commercial development of these natural compounds indicates only minimal commercialization due to the lack of sustainable supply. To bridge the gaps between discovery and commercialization of these tantalizing bioactive compounds, marine bioprocess engineering is the key for its success. The problems, challenges and opportunities for marine bioprocess engineers are examined for the timely transformation of the discovery into commercial reality. Marine bioprocess engineers will find it the most rewarding practice of their expertise in diving into the ocean.

Key words: Marine natural products, Commercialization; Marine bioprocess engineering; Sustainable supply

Introduction

The oceans, nearly three-quarters of the Earth's surface, has proven to be home of a rich source of both biological and chemical diversity that represents a huge potential resource for novel natural products. The search for medicinal use of natural products derived from the sea has a long history. However, until 50 years ago, this resource remained largely untapped before Bergman and Feeney (1951) started the first serious work on studying marine natural products. Since then, there are more than 10,000 compounds that have been isolated from marine organisms (Jaspars, 1998), and a steady growth in the number of patent applications for the past three decades and a rapid increase in the past decade were observed (Figure 1). These patents cover natural products for use as pharmaceuticals, nutriceuticals, cosmetics, agrichemicals, novel enzymes and research tools for the biomedical sciences. Each of these classes of marine bioproducts has a potential multi-billion dollar market value (Pomponi, 1999). Unfortunately, this exciting market value has rarely turned into a commercial reality despite that many endeavors have been made. There is too great a gap between academic research on natural compounds from marine sources and their commercial development. It has been well-known as pharmacopoptosis – "programmed drug death" in the area of marine pharmaceutical development.

In this review, a critical assessment of the current status of commercial development of marine natural products will be presented and the problems and future potentials will be discussed. Marine bioprocess engineering has been realized as the key for bridging the gap from discovery to commercialization. The challenges and opportunities for marine bioprocess engineers are identified.

Current Status of Commercial Development of Marine Natural Products

About 300,000 species has been described in the oceans but they only account for a small percentage of the total number of species that have yet to be discovered and described (Malakoff, 1997). In terms of marine microorganisms, only 1500 marine species has been described over an estimated 1.5 million species. From a relatively small number of these described species, numerous natural products have been isolated and the majority is related to pharmaceutical compounds. Given that the worldwide market in drug derived from terrestrial plants currently valued at US$22bn (Harvey and Waterman, 1998), there is an obvious incentive for companies to tap into the oceans.

The main marine organisms being investigated for their natural products are sponges (Porifera), soft corals (Octocorallia), sea squirts (Ascidiaceae), sea mats (Bryozoa or Ectoprocta), sea slugs (Mollusca) and marine microorganisms (bacteria, fungi and cyanobacteria). Of them, marine sponges are the greatest known source of chemicals with the potential to treat human illness (MarinLit, 1998).

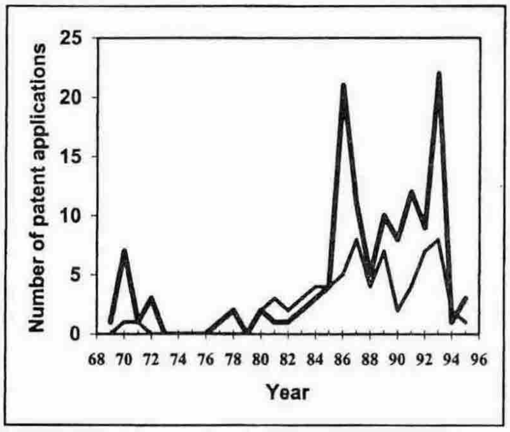

Figure 1. Patent applications by year on marine natural products (Bongiorni and Pietra, 1996)

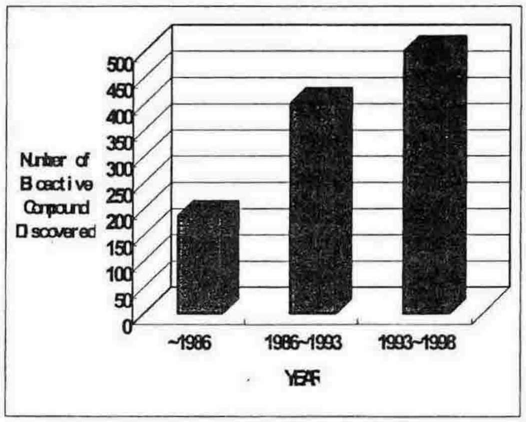

Figure 2. The discovery of bioactive compounds showing cytotoxic properties by year

Over the years, a rich diversity of marine natural products has been discovered with an estimated number over 10,000 that range from antifoulants to anticancer agents. For natural compounds with potential antitumor properties alone, nearly 1000 bioactive compounds were reported up to 1998. It is interesting to note that about 80% of them were discovered after 1986 (Figure 2). The implication is obvious that the importance of marine natural product development is being widely recognized by a number of organizations including the governments, funding agencies, Universities and research institutions, and without doubt the industries over the past decade.

As an application-oriented biotechnology area, it is critical to assess the commercial success of marine natural product against the investment of time and money and optimism in this field. There have been some notable successes in obtaining natural products for commercial and pharmaceutical purposes. Martek Biosciences of Columbia, USA produces docosahexaenoic acid (DHA) for infant formula milk from the bulk cultivation of marine micro-algae *Cryptocodinium cohnii*. Estee Lauder, USA has commercialized the first products from marine invertebrate, anti-inflammatory compound pseudopterosin C for skin care product *Resilience®*. Pharma Mar SA, Spain are currently looking at 111 candidate anticancer agents with only ecteinascidins 743, which is currently in Phase II clinical trial. Nevertheless, the commercial success is rather scattered in contrast to the number of natural products isolated. A typical case is given by the commercial development of anti-cancer marine compounds (Munro et al., 1999). With 1000 in vitro bioactive metabolites available, however only 18 have been tested in vivo and in clinical trials. Up to now, none of them is in clinical use. The crucial problem related to this scarce commercialization is obtaining a sustainable supply for testing, and commercial uses. For marine natural products in general, once the potential applications have been identified they will need to be produced in large amounts for development, test and uses.

The Supply Problem

The supply problem haunts most of the commercialization of marine natural products, and there are several options to cope with it including wild harvest, controlled harvest, aquaculture of the source organisms, chemical synthesis, in vitro production through cell cultures in bioreactors, and transgenic production. Often, the metabolite occurs in trace amounts in the organism, a steady source of supply can not rely on wild or controlled harvest in general. A feasible collection can only be done without damaging the ecosystem. Chemical syntheses have been achieved for many marine bioproducts, however, one has to distinguish between an 'academic' synthesis and an 'industrial' synthesis. Many natural products are complex molecules with several stereocenters, making the synthesis a multi-step process that are not amenable to synthesis in an economic, industrial-scale (Pomponi, 1999). In situ aquaculture of the source organisms, based on a long history of commercial fishery practices, are still the easiest and cost-efficient method of production of the biomass of interest. Successes have been made in aquaculture of the bryozoan, *Bugula neritina* and the ascidian *Ecteinascidia turbinata* for the production of antitumor compound, ecteinascidin 743 (Munro et al., 1999); and the New Zealand deepwater sponge, *Lissodendoryx sp.* for the production of halichondrins (Battershill et al., 1996). However, aquaculture does not afford the opportunity for over-expression of production of the compounds as it is carried out under the unpredictable and often sub-optimal natural environment. The biosynthesis of targeted compounds usually shows a great variability with location, season, and genetic make-up, which further complicates the downstream processing. Hence, a better-defined production system would be desirable. In vitro cell culture (or fermentation) in closed bioreactors is the most desired and promising option for overcoming the supply problem, since this will give the opportunity to use completely defined and controlled systems. However, in vitro bioreactor cultivation is still in its infancy, which is surrounded by many fundamental questions and uncertainties. This remains to the real challenges for the marine bioprocess engineers.

Marine Bioprocess Engineering – Challenges and Opportunities

No matter how attractive a biological profile a marine natural product might have, unless an adequate supply stream can be generated the product will remain of novelty value only. The discovery of a novel compound is just the leading part of the commercialization train. Marine bioprocess engineering, i.e. the application of the principles, methodologies and tools of modern engineering and biotechnology to marine organisms and processes, is the generic applied research area to address the challenges (Zaborsky, 1999). While the importance of marine biotechnology has been widely recognized as one of the four "second wave" biotechnology areas in the United States and many other countries, however the engineering component has been largely ignored, if not intentionally. Fortunately, the lesson from the minimal commercialization success out of the huge number of natural products discovered is leading to a general recognition that marine bioprocess engineering is the critical link from the discovery to commercialization (Zaborsky, 1999).

Marine bioprocess engineering that addresses the generic issues or bottlenecks in marine natural product development is the key for their timely transformation into the commercial success. To build the bridges from discovery to commercialization, the challenges and opportunities exist for bioprocess engineers in different phases included:

Discover phase:

Develop tools or technologies for the sampling of the widest range of bio-diversity (e.g. the unusual habitats in extreme environments) and for rapid, in situ screening and identification of marine organisms and their novel bioproducts.

Development phase:

Develop fundamental understanding of genetic, nutritional and environmental factors that control production of the metabolites in marine organisms, and the basis for sustainable use of the metabolites. Design the fast-track process for supply of products in question for functional test and market development.

Production phase:

Design, development, modeling, optimization and scale-up of sustainable manufacturing bioprocesses including bioreactors for sustainable marine metabolite production; develop the cost-efficient product recovery technology taking the eco-physiological characteristics of marine bioproducts into account; design the bioprocess strategies for maximizing the economic performance of the commercialization.

Conclusions

The ocean represents an incredible rich resource of novel chemicals with potential applications in almost every major industrial sector including health, environment, energy, food, chemicals, advanced materials and national defense. Commercial application of marine natural products has been hampered by our limited marine bioprocess engineering skills that is being recognized as the highest priority to be pursued for bridging the gap from discovery to commercialization. Successful addressing the challenges will provide great opportunities for bioprocess engineers to play a key role in the commercial development of a myriad of marine natural products with benefit to many of the society.

Acknowledgements W. Zhang wishes to thank the Chinese Academy of Sciences and Dalian Institute of Chemical Physics (Dalian) for financial support under the "100 Talent Project".

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