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Commentary

A renaissance in marine pharmacology: From preclinical curiosity to clinical reality

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ABSTRACT

Marine pharmacology, the pharmacology of marine natural products, has been for some time more associated with marine natural products chemistry rather than mainstay pharmacology. However, in recent years a renaissance has occurred in this area of research, and has seen the US Food & Drug Administration (FDA) approval in 2004 of Prialt® (ziconotide, ω-conotoxin MVIIA) the synthetic equivalent of a conopeptide found in marine snails, used for the management of severe chronic pain. Furthermore Yondelis® (trabectedin, ET-743) an antitumor agent discovered in a marine colonial tunicate, and now produced synthetically, receiving Orphan Drug designation from the European Commission (EC) and FDA for soft tissue sarcomas and ovarian cancer and its registration in 2007 in the EU for the treatment of soft tissue sarcoma. The approval/marketing of so few marine natural products has come after many years of research primarily by the academic community and the sporadic involvement of major pharmaceutical companies. This commentary, through the opinions provided by several leaders in the marine natural products field, will examine the potential reasons and perceptions from both the academic and pharmaceutical communities regarding the development of marine natural products as viable therapeutic entities.

Marine Natural Products (MNPs) offer an abundant source of pharmacologically active agents with great chemical diversity and complexity, and the potential to produce valuable therapeutic entities. The realization of this potential through the recent approval of two MNP therapeutics has taken many decades.

The potential of marine natural products has captivated many researchers over the years. Inspired by the vastness of our oceans, and an almost incomprehensible level of biodiversity in the marine environment, researchers have enthusiastically pursued the pharmacological potential of secondary metabolites from marine organisms. This is reflected in the numerous reviews on this subject matter in the past ten years (705 PubMed references for marine pharmacology as of January 2009)[1] and that currently there are some 13 MNPs in some Phase of clinical development (http://marinepharmacology.midwestern.edu/), and more on their way. It has been almost five decades since the isolation of spongothymidine and spongouridine from the marine sponge *Tethya crypta* by Bergman [1–3] that eventually led to the development of Ara-C (cytarabine, an antileukemia agent) and Ara-A (vidarabine, an antiviral agent), agents which received FDA approval in 1969 and 1976, respectively. Since the approval of Ara-C and Ara-A as therapeutics, it was not until 2004 that the next MNP would be approved, ziconotide (Prialt®), for the treatment of severe chronic pain [4]. This was soon followed by the orphan drug status granted to trabectedin (Yondelis®) for the treatment of soft tissue sarcomas and ovarian cancer, and its registration in 2007 in the EU for the treatment of soft tissue sarcoma [5]. However, the approval of so few marine natural products has come after many years of research primarily by the academic community and sporadic involvement of major pharmaceutical companies (Fig. 1).

These few approvals have not been due to a lack of discovery of novel marine natural products. Faulkner [6–8], Blunt et al. [9–14], and Mayer [15–26] have provided comprehensive reviews of the total number of marine natural products discovered (D.J.F. and J.W.B.), and those with significant preclinical and clinical pharmacological activity (A.M.S.M.) for the years 1998–2006 (Table 1). MNP pharmacology has evolved from, in the early years, broad surveys of

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[1] MarinLit database, http://www.chem.canterbury.ac.nz/marinlit/marinlit.shtml, provides a more comprehensive view of MNPs.

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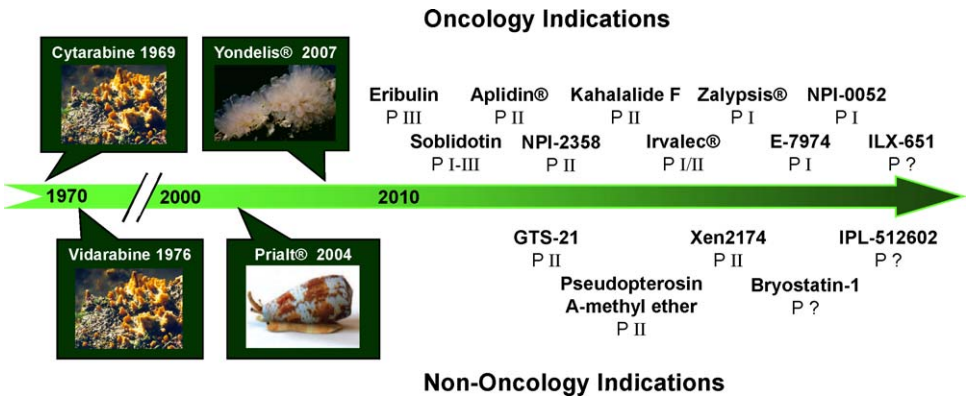

Fig. 1. Clinical development timeline for MNPs. After isolation in the 1950s and approval in 1969 (Ara-C, cytarabine) and 1976 (Ara-A, vidarabine), these MNP derivatives have been the only MNPs in clinical use. In 2004 with the approval of ziconotide and in 2007 of trabectedin, the promise of more MNPs as therapeutics appears to be imminent.

marine life for novel MNPs providing many novel chemical entities regardless of pharmacological activity into what currently is considered the targeted approach to drug discovery, focusing on specific diseases (e.g. cancer, inflammation, etc.), and molecular targets (e.g. specific enzymes and receptors). Early assay guided fractionation of marine extracts was hampered by limited ability to dereplicate those extracts from known MNPs, an issue which can now be expedited with continued improvements in the technology to identify and elucidate MNP structures, and has become more commonplace in MNP laboratories [27]. Even with these developments and the intense interest in marine pharmacology prior to the year 2000, some of the leaders in the field of MNPs were contemplating "Where are the drugs?" [28]. In the years from 1995 to 2005 efforts appeared to refocus through agency-supported initiatives with the Cooperative Drug Discovery Program of the National Cancer Institute (NCI) playing a key role, and with major pharmaceutical companies deemphasizing natural products research, this paved the way for the development of more productive collaborative efforts between academia and the pharmaceutical industry that eventually translated into clinical trials [29], and eventually several marketed MNP derived therapeutics. Several factors that have influenced this renaissance in MNP are the technological developments that have aided in structural elucidation, screening, the possibility of using marine microbial/fungal genomics to provide biosynthetic pathways for MNPs, and the failure of alternate technologies such as combinatorial chemistry to provide the pharmaceutical industry with the chemical diversity necessary to increase significantly the number of new drug-like leads [30].

Surveying the comments provided by leaders in the MNPs field (see below) common themes of the factors that have and will influence the development of MNPs are evident: (1) greater difficulty in collecting and isolating novel MNPs, (2) ability to elucidate the mechanism of action of novel biologically active MNPs through innovative pharmacological studies, (3) how MNPs fit into the high throughput screening (HTS) paradigm used by most pharmaceutical companies to discover leads for novel drug targets, (4) high risk nature of MNP relative to traditional synthetic avenues or terrestrial NPs, (5) the need for strong and productive collaborations between academia and pharma, (6) a better understanding of the natural function of these secondary metabolites (chemical ecology), and a very important factors being (7) the ability to provide sufficient quantities of the MNP for the compound intensive development process and (8) improved methodologies to synthetically convert natural product scaffolds into optimized drugs (Fig. 2).

Generally, early studies on mechanism of action and initial pharmacological characterization utilize relatively little compound; however, upon identification of its therapeutic potential and late-stage preclinical development the compound demand

Table 1
Summary of MNPs identified and characterized between 1998 and 2006.

Year[a]	Chemistry and synthesis of marine natural products[b]	Preclinical and clinical marine anticancer pharmacology[c]	Preclinical and clinical marine pharmacology[d]
2006	779 [10]	136 [18]	183 [25]
2005	812 [9]		
2004	716 [14]	150 [17]	166 [23]
2003	656 [13]		
2002	677 [12]	97 [16]	106 [21]
2001	683 [11]		
2000	869 [8]	143 [15]	78 [20]
1999	881 [7]	31 [22]	66 [19]
1998	841 [6]	35 [24]	67 [26]
Total	6,914	592	666

[a] Year of publication of articles reporting new marine natural products and/or preclinical and clinical pharmacology, and included in the corresponding annual review.
[b] Number of novel marine natural products included in the respective annual review.
[c] Number of marine natural products for which novel preclinical and clinical antitumor and cytotoxic pharmacology was included in the corresponding annual review.
[d] Number of marine natural products for which novel preclinical and clinical pharmacology was included in the annual review. Marine compounds demonstrated anthelmintic, antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; also affected the cardiovascular, immune and nervous systems, and presented several other miscellaneous mechanisms of action.

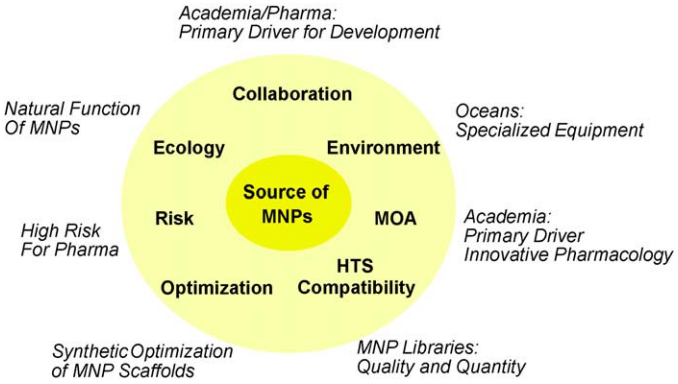

Fig. 2. Common themes and key issues in the development of MNPs. At the center of issues raised by the contributors is the supply of MNPs (Source of MNPs) for clinical development. The other issues raised are then all inter-related to this central issue and to each other in the development of MNPs as therapeutics.

increases almost exponentially. As many, if not all, MNP chemists and pharmacologists are keenly aware of the ecological impact of collecting marine organisms to provide sufficient quantities for clinical development, the ability to provide sufficient material for development has always been a key issue. Organic synthesis of MNPs has always been challenging as these generally complex and highly chiral structures have been optimized by environmental selection pressures over millions of years, utilizing multiple enzymatic synthetic pathways to produce the optimal biological function that provides the species with a key pro-survival benefit. In recent years, the realization of early hypotheses on the origin of many MNPs, as being secondary metabolites of symbiotic microorganisms, has provided an avenue for "relatively" abundant sources of some MNPs. The relatively recent implementation of mariculture of marine bacteria, fungi and invertebrates has mitigated some of the concerns on providing sufficient compound for late preclinical and clinical development. Actually the breadth of marine fungal and bacterial species has been underestimated in the past [31–34] and could provide a substantial source for newer and more obtainable MNPs for development [35–37]. The promise of unlocking the microbial/fungal genome to identify pathways that could be tailored to provide a unique and potentially fruitful novel set of MNPs, those that cannot be identified under routine laboratory screening for MNPs, has been demonstrated with the sequencing of genome of *Salinospora tropica* [38,39]. The potential use of combinatorial peptide libraries to diversify and optimize the drug-like properties of peptides, coupled with innovative delivery methods has great potential to provide novel MNP therapeutics, especially with the diversity seen in *Conus* sp. peptides [40,41].

These recent developments in MNPs research and the continued enthusiasm for MNPs as leads for therapeutic compounds, along with the approval of Prialt® and Yondelis®, has generated a "Renaissance" in marine pharmacology, and the potential that these natural products hold for the armament of therapeutics needed to treat human disease. As such we have asked several prominent leaders in the field of MNPs to comment on the field, and what in their opinion has enhanced or hampered the development of MNPs. Overall, as you read the opinions of these individuals, it is clear that the enthusiasm for discovery and development of MNPs has not been dampened by their experiences or the impediments of performing this type of novel drug discovery. These views come from a mixture of academic and industrial perspectives; the academic view often is also reflective of interactions with both pharmaceutical and biotech companies and some of these individuals have moved from academic to industrial positions, thus providing unique perspectives on the development of MNPs.

(I) The first group of contributors (W. Fenical, C.M. Ireland, R.S. Jacobs and M.T. Hamann) provide a perspective on how US based academia view developments in the field of MNPs; these contributors demonstrate the essential role academia has played in the development of MNPs, and the need for productive ties to the pharmaceutical industry as the avenue to ensure the development of MNPs as therapeutics:

William Fenical, distinguished Professor and Director of CMBB, The Scripps Institution of Oceanography, University of California at San Diego contributed his thoughts on: *Marine Drug Discovery, A History of Difficulty*.

> "Since the field of marine natural products chemistry began in the mid 1960s, it has been clear that the oceans and their diverse biota represent a significant resource, perhaps the greatest resource on Earth (34 of the 36 phyla of life), for the discovery of new drugs. During the first decade of this science (ca. 1970–1980), researchers explored the oceans to discover the specific biological taxa that would yield bioactive molecules. Hundreds of structurally-novel, bioactive molecules were discovered proving that marine organisms had the potential to be developed into drugs in many areas of human therapy. There were problems, however, that hindered marine drug discovery. First and foremost, was the fact that the ocean was a completely unknown environment and one that was considered hostile and "beyond the realm of drug discovery". While the pharmaceutical industry was intrigued, they lacked the confidence to make the major financial investments that they had made in terrestrial microbial drug discovery (at one time $ 9B/yr) and in plant related research. It was just too far out, plus there was little evidence to show that this would succeed. It was safer to continue on the same course.
>
> In the mid 1980s, the situation slightly changed and small investments were made by big pharma in marine natural products research. Some of the major companies collaborated with academic researchers and successes began to be observed. Still, the degree of investment was minor and only a few tangible discoveries made their way to clinical trials. The situation was about to change, as the National Cancer Institute discovered that bioassays with marine organism extracts were far more likely to yield anticancer drugs than terrestrial sources. This realization resulted in significant financial support to the academic community for the discovery of anticancer drugs, and with the exception of some collaborative programs, industry was largely uninvolved. As time passed, industry invested in only minor ways. It became clear that significant investment, equivalent to investments made in other areas, would not be forthcoming unless pharma brought this area in house. With a few minor exceptions, this never happened and marine drug discovery remains to this day largely an academic pursuit.
>
> What have been the problems? Certainly it has not been the structural uniqueness and interesting pharmacological activities of marine compounds. I believe it was that perceived risk was high and there was little support from management who lacked familiarity with the oceans. Of course, there were other problems. One major problem was drug supply. The discovery of a new drug candidate requires only minor amounts of material. But, as the compound progresses into development, larger and larger amounts, grams to kilograms, of compound are a necessity. It was simply not feasible to collect the hundreds of kilograms of animals, frequently from pristine coral reef environments, to satisfy this need. At the same time, the synthesis of natural products was difficult, as most natural products are chiral and possess complex structures. In a reasonable fashion, pharma needed to prioritize their lead structures with availability as an important criterion. Also, during the period of the 1980–1900s, the concept of combinatorial chemistry overwhelmed the pharmaceutical industry. Combinatorial methods promised to provide the answer to the enormous numbers of compounds needed for the robotized high throughput screening (HTS) technologies that were in development. Natural products, most often available in small amounts and in limited numbers, simply didn't fit that paradigm.
>
> With growing competition world-wide and investors anxious for continued high profit, the pharmaceutical industry found itself in a situation that was solved, at least temporarily, by mergers. The intense pressure was to find and develop more profitable drugs, i.e. block buster drugs, which is still the norm today, created urgency and changed the timeline for drug development. The standard processes of natural product collection, extract preparation, screening, bioassay-guided purification were simply too slow and unresponsive to the new standard for drug discovery and development. Marine natural products, in particular, with its problems in recollection

and structure modification, became even further detached from the drug discovery process.

The situation hasn't changed in 2008; the major US pharmaceutical industries continue to move in directions that do not facilitate the incorporation of marine natural products. However, there is one major development that is changing the ways in which drugs are discovered. More and more today, big pharma is relying on academic laboratories, research institutes, and small biotech industries to undertake drug discovery. In-licensing drugs is now a major component of the pharmaceutical industry, and this has led to a resurgence in the discovery of drugs from natural sources. Biotech industries in the US and Europe have now successfully discovered, clinically developed and marketed marine-derived drugs, ultimately with big pharma as a partner. Three marine drugs are currently on the market for intense pain, and for the treatment of cancer. Many more (ca. 25) are on their way.

The biotech industries of the new millennium are not risk averse. Funded largely by venture money, these industries take the risks that big pharma was previously unwilling to accept. Biotech companies have been established that now explore the world's oceans, both shallow and deep. In addition, new marine sources are being identified that have the ability to lead to new drugs in areas currently lacking significant big pharma investment. Within the past decade, we have recognized the potential of marine microorganisms as a new pharmaceutical source, including new antibiotics for the treatment of drug-resistant human pathogens. Unlike the collected sources for marine compounds (sponges, ascidians, etc.), the isolation of marine bacteria and fungi do not impact the environment. Through established culture methods, these organisms can produce the kilograms of drugs needed for structure optimization, clinical trials and marketing.

Other scientific advancements continue to make investment in marine compounds more attractive. Although difficult to collect in quantity, the amazing advances in synthetic chemistry have provided access to even the most complex of drug lead structures. Very complex compounds have gone from discovery to clinical trials based upon the strength of the industrial chemists who have demonstrated the power of multistep, chiral total synthesis.

Where from here? In this author's opinion, the discovery of new drugs will continue to diversify. Academic entrepreneurs, research laboratories and innovative biotech industries will play an even greater role in the discovery of new drugs."

Chris M. Ireland (Professor of Medicinal Chemistry and Chair), Tim S. Bugni, Mary Kay Harper from the Department of Medicinal Chemistry, University of Utah, contributed their opinion on the development of MNPs:

"Converting the promise of "drugs from the sea" to reality has been a long and often frustrating process marked by ebbs and flows of enthusiasm from both funding sources and the pharmaceutical industry. It has just been in the last couple of years that the first therapeutics, Prialt® and Yondelis® have been approved for human use. In principle, the process of sourcing new pharmaceuticals from marine organisms is no different than other natural sources, or even purely synthetic chemical libraries. The early discovery phase focuses on identification of new chemical entities with defined biological effects. The second or preclinical development phase focuses on optimization of pharmacodynamic and pharmacokinetic properties in animal models, and the third or clinical development phase focuses on efficacy and safety studies in humans. However, in practice these three phases have been implemented very differently in the marine pharmaceutical realm. Whereas big Pharma has actively embraced all three phases of drug discovery and development involving new drug entities from synthetic chemical libraries and microbial natural products, or even plant based natural products, it has invested very little effort in the early phases of drug discovery from marine organisms. This is in spite of the fact that marine organisms have proven over the years to be the source of an unprecedented array of structurally complex and unique chemical classes often with very high potency and selectivity for biological receptors.

Although there have been a few exceptions, perhaps the most notable being the now defunct Roche Research Institute of Marine Pharmacology, the consequence of big Pharma's lack of interest has been that the overwhelming majority of early drug discovery research in marine natural products has been performed in academic research programs. For example, twelve of the fourteen marine derived drug candidates currently in clinical trials for oncology can be traced directly to compounds discovered in academic laboratories.

In essence discovery of drugs from the sea has become an academia-centered cottage industry. This somewhat unique situation in drug discovery and development has actually had its benefits and pitfalls. Although big Pharma has not invested in the early stages of the process, they have shown willingness to tap into the pipeline once value has been demonstrated, an often necessary contribution to offset the exorbitant cost of drug development. This has led to a number of strategic alliances between academic groups and big Pharma companies and also academic groups with small to medium sized biotechnology companies. A number of these alliances that marry the discovery engine provided by the academic groups with the development capabilities of the companies have proven very fruitful. One such example is the National Cooperative Drug Discovery Group (NCDDG) program developed and funded by the National Cancer Institute. Over the years the NCDDG mechanisms have supported collaborative marine natural products based consortia at Cornell with Bristol Myers Squibb, several University of California campuses with BMS and Novartis, and the University of Utah with Wyeth. Additional examples of productive alliances include Pharma-Mar's programs with academic groups in the United States, New Zealand and Japan, Astra Zeneca's collaboration with Griffith University, and Nereus Pharmaceuticals with Scripps Institution of Oceanography.

An academic front end to the drug discovery engine has also presented its own challenges. Because funding for many of these academic groups has come largely from federal sources there have been issues with continuity and productivity as a result of the whims associated with competitive funding decisions at a national level. These include shifting priorities and shrinking budgets during economic downturns. Also, because the academic paradigm has traditionally been publish or perish the early transition towards technology commercialization was a rocky one on numerous campuses with many compounds making it into the published literature before their drug potential could be properly assessed or legally protected. All in all the system is not optimal, but does seem to work at some level based on the recent successes in the field and a growing pipeline. With the failure of combinatorial chemistry to be the "cure all" for accessing diverse chemical space and identifying leads with drug-like properties, there is still an important role for nature in providing unique chemical scaffolds as starting points for drug discovery. We believe the successful paradigm for the future will be to combine nature's amazing ability to produce unique scaffolds, many of

which already possess high potency and receptor affinity with the power of medicinal chemistry to optimize the pharmacokinetic properties of these molecules and their affinities for therapeutically relevant receptors. This model has already been successfully applied to numerous marine natural products such as hemiasterlin, psammaplin A, halichondrin B and the dolastatins to generate clinical candidates. Also as all of the above examples illustrate, this approach can have the added benefit of generating drug candidates that are synthetically accessible thus addressing a long standing concern about sourcing in marine natural products drug discovery. In the future these hybrid approaches along with advances in genetic engineering will completely negate the issue of supply of marine natural products for drug discovery and development."

Robert S. Jacobs, Professor, The Department of Ecology, Evolution and Marine Biology, University of California, Santa Barbara, contributed his opinion:

"My own experience at G.D Searle has colored my view to the extent that it may be very much out of date. My subsequent experience as an academic provided a somewhat different view. The early products of Drug Companies were generally crude extracts and powders in which the product was labeled in Latin or English reflecting the name of the plant of origin. Pharmacology laboratories were developed as quality control laboratories using animal models that in some cases did not necessarily always reflect a sensitive model detecting only one active ingredient. They were developed to assure the equivalent activity. Early in the 20th century various companies began efforts to isolate and purify the active ingredients in hundreds if not thousands of extracts using bioassay guided isolation and purification. Soon after World War 2 ended drug companies began marketing pure materials and later synthetic compounds. The discovery of cortisone and penicillin caused stunning reactions in the medical community (Wonder Drugs was the buzz word). In that particular time period all new drugs were from natural sources and acquired from academic studies or from field expeditions in search of discovery of new plants. The pipeline was always full and drug research laboratories became a focus of interest in many countries. Lab models were almost always animal-based except for antibiotics. The source of discovery was some times folklore, physicians, traveling salesman selling roots from a wagon (Gideon Searle?), military occupation of a foreign country, or even adventurers and explorers (Indiana Jones Types). There was no FDA, GMP, Market Researchers, or evil Stock Market Analysts present to comment on the marketing of a new wonder drug particularly when the market is small.

The number of drugs entering the clinic per month was very substantial many (most) however fell out and did not advance to market because of sometimes poorly understood side effects or toxicity and poorly developed experimental evidence that would validate their being acceptable for a particular application. The American Medical Association was the primary reviewer panel analyzing drug efficacy. The USP provided standardized formulation guidelines.

In my lifetime I have observed the huge impact of organic chemistry, biochemistry, and pharmacology on drug discovery and development. There is no question that the drug industry took the lead in product development. Along with the invention of Scuba however the ocean became a new target of discovery that opened up new and unexplored opportunity. The academic scientist (Indiana Jones Type) also faced a series of hurdles including a powerful and efficient center of chemical and pharmacological excellence in the Drug Industry, an overwhelming pre-existing patent portfolio (prior art) and an institutional bias in Academia. The latter has to do with the ethics of a non profit employee (Chemistry or Biology professor) creating intellectual property for a business. This ethics issue has largely disappeared with Universities developing Tech Transfer Offices that have become pretty successful. The Indiana Jones type nowadays has a PhD in Chemistry or Biology and can understand navigation (we hope). His slide rule is a lap top; he travels with gallons of solvent and a TLC plate. Early on one could not help to speculate that most marine plants and animals may actually produce chemistry already discovered from terrestrial sources or conceived theoretically by a chemist, biochemist or pharmacologist as a logical intermediate or product of something found elsewhere. That is the case with marine natural product development. That is also in part because patent law allows considerable latitude in claiming chemistry and on biological uses. This can cause a drug company to not pursue a discovery because the chemistry is common and not too unique. In other words the opportunity for chemical development had limited scope. Another problem is that often the area of clinical interest to the company has nothing to do with their current product discovery/development goals. In other words there is no immediate opportunity for development beyond discovery information. What is in the pipeline if anything is usually kept secret.

Most recently I have observed that there have been substantial mergers among the larger companies. Searle became Monsanto, Monsanto became Pharmacia, Pharmacia became Pfizer. Syntex is now Roche, SKF became Glaxo, etc, etc. This contraction has lead to the loss of the many individual experienced chemists and biologists in the smaller companies along with their future contribution to the "pipeline". The academic scientist also has in many ways lost contact with the industrial scientists. Decisions on drug development options may take place outside of the U.S. I think this merger stuff is among the most serious threat to seeing new drug pipelines emerge. Certainly the stability of career development of highly specialized scientists and the US industry is at stake.

Considering all of these factors it is surprising there is still progress ongoing and discovery continues. Academic biologists and chemists are best advised to collaborate on the mechanism of action of a drug as a very necessary step in attracting development interest. Developing startup companies is also a growing activity nation wide."

Mark T. Hamann, Professor of Pharmacognosy, Pharmacology, Chemistry and Biochemistry, and the National Center for the Development of Natural Products, The University of Mississippi and Triton BioPharma, Oxford, Mississippi, contributed his opinion on: *Marine natural products development. Recent progress and remaining challenges*.

"Recent years have yielded significant achievements and progress for the field of marine natural products and drug development as exemplified by the successful approval of commercial products from cone snails (Prialt®) and ascidians (Yondelis®) for the treatment of pain and soft tissue sarcoma, respectively. Over a half century has passed since the first discovery of spongothymidine and spongouridine which ushered in the highly successful enterprise of modifying nucleosides as antiviral and anticancer chemotherapy as well as the exploration of marine samples globally for additional prototypes for the control of disease. These sponge derived nucleosides initiated a chain of events in discovery and development that have resulted in countless saved lives from viral infections and cancer. The natural products chemistry

inspired from these early discoveries has been unprecedented in regard to structural complexity and biological significance and indeed tremendous opportunities still remain. There has been a tremendous number of advances to aid in the development of resources from the ocean and include improvements in technologies to collect, purify, characterize, synthesize, optimize, assay and at greater scale. However despite the continued improvements in the tools for drug discovery and development the critical key ingredient that is consistently present is a champion or group of champions with a vision for discoveries made at the bench. If there is anything that I am compelled to emphasize regarding the past accomplishments in the field of marine natural products and marine pharmacology it would be to applaud those individuals with the vision, energy and determination to move the leads which in the beginning are always sketchy at best through the development process to create a meaningful treatment for human disease.

While the advances in technologies to develop marine drug leads combined with recent success stories is certain to fuel enthusiasm for the development of marine products there are indeed challenges that remain. Among the most attractive features of marine natural products continues to be the structural diversity of secondary metabolites including the incorporation of elements like bromine rarely found in terrestrial secondary metabolism. This structural diversity and complexity brings with it clear challenges in the production of sufficient material in order to make an informed decision in regard to the utility of a molecule. Continued advances in synthetic approaches as well as a focus on marine microbes and invertebrate associated microbes slowly whittles away at these limitations. Perhaps one of the most significant challenges which remains and is in essence growing with each discovery and are the growing expectations associated with the pharmaceutical industry as a whole. With each new approved drug comes raised expectations for safety and novelty for the new drugs of the future. While this is an inevitable and highly beneficial outcome for the consumer the rising bar in drug development will continue to create growing challenges for those in all fields of drug discovery and development. The end results are clear and indicate that the field of marine natural products will continue to play an increasingly significant role and provide novel materials for the construction of the drugs of the future however the application of these materials as pharmaceutical products will require greater and greater efforts to transform these natural building blocks into safer and more effective and innovative pharmaceutical products."

It is evident from the above opinions that the contribution of the larger pharmaceutical companies has been at best sporadic and that the primary source of new developments in MNPs has come almost exclusively from the academic sector. This academic focus potentially stems from an aversion to higher than normal risk associated with the development of MNPs, both real and perceived factors, by the larger pharmaceutical companies. Key to the recent development of MNPs has been the collaboration of academic scientists with the less risk adverse smaller biotechnology companies to foster the late-stage preclinical and initial clinical development of these MNPs, which then provides the biological data necessary to potentially merge development of these MNPs into the pipeline of medium and large pharmaceutical companies who are always looking to fill clinical pipelines with promising new chemical entities.

(II) The second group of contributors (M.J. Alcaraz, M. Jaspars, and N. Fusetani) reflects the common concerns and issues faced by international academia in the development of MNPs outside of the US:

Maria J. Alcaraz, Professor of Pharmacology, Department of Pharmacology, University of Valencia, Spain, contributed her thoughts on the development of marine natural products:

"Marine natural products have been the focus of intense research activity revealing the high potential of the marine ecosystem in the discovery of new bioactive agents. There is increasing recognition of the role that academia has played in the preclinical phases, leading to spin-offs or partnering with industry for further development. Unfortunately, in many cases, interesting contributions to basic research and knowledge have not been translated into drug development.

A key characteristic of marine pharmacology is its complexity. The identification of new targets and the discovery and evaluation of drug candidates have been hampered by scarcity of naturally available material, chemical synthesis procedures which may be difficult economically, problems in the culture of marine organisms, presence of phytosymbionts in marine organisms or inconsistent production of active metabolites in cultures.

However, despite initial enthusiasm, the availability of public funding for marine research has fluctuated in some countries. In the last years, given the challenges involved in developing effective therapeutic agents, marine drug discovery has been scarcely supported by government agencies as a consequence of policies addressing other innovative research approaches.

On the other hand, industrial institutions with an inherent focus on product development have experienced in recent years a number of difficulties in this increasingly complex and uncertain task. Financial constraints aside, problems such as short commercial half-lives of drugs and regulatory hurdles have contributed to reconsideration of interest in the research and development of natural products including those of marine origin.

There is a great deal yet to be learned about marine pharmacology. Drug discovery programs should take advantage of the tremendous biodiversity present in the marine ecosystem. Industry and government agencies should be increasingly aware of the potential of marine organisms as a source of therapeutic innovation. Progressing research efficiently across this complex field requires multidisciplinary initiatives to bring together diverse expertise as well as the application of novel technologies. Concerted efforts of government agencies, industry and academia leading to closer research collaboration are essential to achieve the development of innovative medicines of marine origin."

Marcel Jaspars, Professor and Chair of Organic Chemistry, The Marine Biodiscovery Centre, University of Aberdeen, Scotland, UK and Science Manager for Marine and Aquatic Biotechnology for the Bioscience for Business Knowledge Transfer Network provided the following opinion:

"Major funding by government agencies in the US has led to a reappraisal of natural products as a source of new pharmacophores in the last few years, but mainly with applications in the treatment of cancer. Other fields in which natural products have a historical track record have remained relatively under-investigated in marine pharmacology over the same period, particularly anti-infectives and anti-inflammatories. Stimulation by national governments to re-investigate the potential of natural products as anti-infectives is necessary to spur the pharmaceutical industry back into discovering treatments for this disease area [42].

Marine sources have been shown to be of particular interest, as their coverage of chemical property space is the broadest and therefore their potential as pharmaceuticals is unparalleled [43]. What needs a greater focus is acquiring a deeper understanding of the native functions of these metabolites and the advantages they confer on the producer. A polyphasic approach is necessary, using genomics, chemoinformatics, molecular genetics and chemical ecology studies as well as allied disciplines. This knowledge will lead to a more targeted approach to accessing those organisms which have the greatest potential for producing pharmacophores for particular disease states. On top of this, a greater understanding of the fundamental physiology of marine invertebrates and microorganisms is necessary [44], with examples being the acquisition of metals by marine invertebrates and the change in secondary metabolite biosynthesis in marine bacteria in response to high pressure. Novel discoveries in both these areas have the potential to lead to new treatments for disease, for instance, bacterial infection [45].

Generic technologies which accelerate biomedical research and assist in drug development and delivery also have a great potential to make an impact. A key example is of course the investigation of conotoxins for academic reasons and their subsequent application in the treatment of pain and other diseases. Their applications have reached beyond this in the investigation and understanding of mammalian ion channels. Another technology which is being developed is a generic molecular delivery tool based on the marine sponge-derived poly-alkylpyridinium salts, which can be used to deliver drug molecules, cDNA and large proteins into the intracellular compartment with consequent applications for research and medical applications [46].

An area where academic interactions are important is technology transfer to biodiversity-rich source countries. Academic investigators in this area have developed links with scientists in source countries over a long period of time, and have been heavily involved in the creation of access and benefit sharing legislation together with government agencies such as the US National Cancer Institute and the Australian Institute of Marine Science. These links have led to novel discoveries, jointly owned between the parties and the exchange of staff and students with major benefits to the visitors and the hosts. The biodiscovery landscape has changed enormously over the last 15 years, but new legislation separating access and benefit sharing should make it possible to continue to investigate the potential of novel marine species from unexplored habitats."

Nobuhiro Fusetani, Professor, Graduate School of Fisheries Sciences, Hakkaido University, Japan provided his opinion on: *Marine Pharmacology/Marine Natural Products.*

"The 40-year marine natural product research has proved that marine organisms are valuable sources of potential drugs as well as of important molecular probes for life science research. I would like to emphasize the contribution of marine natural products (MNPs) to basic research as research tools, especially toxins, such as tetrodotoxin, kainic acid and okadaic acid. More and more marine natural products will be used to elucidate biological processes. However, modes of action studies have been carried out for a very limited number of MNPs, which is perhaps due to sample supply and funding. We must encourage marine natural product chemists to collaborate with pharmacologists or biochemists in modes of action studies.

Obviously, the most serious problem in drug discovery from marine organisms is the supply of samples, which is an obstacle to SAR studies, chemical modification to more efficient and less toxic analogues, and of course preclinical and clinical trials. Chemical synthesis is not mature enough to prepare large amounts (kilograms) of complex molecules. Aquaculture is not realistic. The most promising and realistic solution is to isolate biosynthetic genes of candidate molecules or to cultivate MNP-producing microbes, since many promising MNPs are likely produced by symbiotic microorganisms. It is therefore surprising that only a small number of researchers are involved in such research, which is perhaps due to the difficulty in obtaining research funds.

Most big pharma have quit exploring drugs from natural products, which apparently affected the value of (or our enthusiasm for) natural product research. This is also true for MNP research. The approval of Prialt and Yondelis has not changed this situation. Seriously, many MNPs that had been under clinical trials were dropped recently. We need a really "good one" for the revival of marine natural product research. In order to realize this, we must accumulate our basic knowledge about marine organisms, including taxonomy, biology, ecology, etc, in addition to those mentioned above."

(III) The third group of contributors (B. Potts and G.T. Carter) provides an industrial perspective on the development of MNPs. Their opinions reflect the optimism that MNPs have the potential to provide valuable therapeutics, and that the issues and concerns with the development of MNPs are being solved over time:

Barbara Potts, Vice President of Chemistry and Oncology, Nereus Pharmaceuticals, San Diego, provided the following opinion:

"A cooperative spirit between academia and dynamic pharmaceutical companies has been critical to the pharmaceutical development of marine natural products. The number of publications on new marine natural products continues to grow [10], largely at the hands of academic researchers and long after efforts to pursue this resource were all but abandoned by big pharma. The quality of the research only improves as technology continues to evolve. Academic labs have taken it upon themselves to develop and implement more sophisticated tools for the rapid dereplication of known compounds [47], to generate high-throughput screening-friendly libraries [48], and to expand their collaborations to identify the biological targets of the new compounds that they discover, or to discover new targets or specificities for previously described compounds [49,50]. Once intellectual property is solidified, the challenge for the university professor then becomes how to get this discovery into the hands of a professional pharmaceutical development team that is going to be its true champion. Some professors have taken to founding their own companies to ensure that this connection is made.

NPI-0052 (salinosporamide A), a potent 20S proteasome inhibitor currently in Phase I clinical trials for the treatment of various cancers, makes for a great case study of a marine natural products success story involving a truly cooperative effort between academia and industry [51]. The compound and producing organism *Salinispora tropica* were discovered by William Fenical's laboratory at the Scripps Institution of Oceanography (UC San Diego) [52]. Fueled by excitement about the structure and the early biological activity data, Fenical and Jensen brought their discovery to the attention of Nereus, who licensed the compound in 2001. As the mechanistic and preclinical findings unfolded, Nereus became increasingly enthusiastic about championing the molecule's journey to the clinic, and the entire development program was undertaken with a very high level of intensity. This required raising awareness about the compound within the investment

community and ultimately securing the commitment of investors to finance the development effort. The development milestones continue to be met as a product of the quality of the molecule at the hands of a committed team of experts. A small, focused company will take great care to overcome the challenges that a new chemical entity may present. This may not be the case when a potentially challenging compound is viewed by a large company with many projects competing for resources. For example, cGMP manufacturing of pharmaceutical grade drug substance by saline fermentation had not been previously demonstrated and thus might have put NPI-0052 in the 'no' checkbox for a different type of pharmaceutical organization. For a highly focused company like Nereus, the viewpoint was simply to rise to the occasion: the talent and expertise to achieve this technical milestone were built into the organization, and a significant effort was undertaken to identify contract research organizations that were willing to work collaboratively on previously unexplored manufacturing processes. Large scale manufacturing of the active pharmaceutical ingredient (API) from *S. tropica* demonstrates that saline fermentation is a viable pharmaceutical manufacturing process and that marine natural products of microbial origin need not be limited by the "supply issue". Similarly, the beta-lactone functionality of NPI-0052 might have been considered a stability liability, but the scientific team developed strategies that ensured the structural integrity of the drug substance over a wide range of processes, including API manufacturing, formulation development and pharmacokinetic analysis of patient blood samples. Having overcome many of the hurdles that might have seemed too extreme early on for the risk-averse, NPI-0052 now stands among other high potential new chemical entities, despite, or perhaps ultimately because of, its marine origins."

Guy T. Carter, Assistant Vice President of Chemical Technologies, Wyeth Research, Pearl River, NY, provided comments from an industry perspective: *Marine Natural Products as a Source for New Drugs—A Pharmaceutical Industry Perspective*.

"The development of major new pharmaceutical products to address unmet medical needs is an exceptionally high-risk venture. To offset these odds, major pharmaceutical companies plow an inordinate proportion of their revenue back into R&D. Owing to the great uncertainty associated with this business Big Pharma must balance the risk of development projects in their portfolios. The escalating costs associated with clinical programs alone discourage all but the most promising programs advancing through pre-clinical development into full-scale development.

Concurrent with this constrained financial picture is the disappearance of intramural natural products discovery programs in favor of HTS-driven synthetic medicinal chemistry. Such programs have proven highly effective at delivering potent and selective candidates into the drug development pipeline. In this context how can a structurally complex marine natural product (MNP) candidate hope to survive?

To answer this question fairly one would have to acknowledge that the odds are stacked highly against successful progression of such an MNP. Only in those cases in which the MNP has compelling biological activity and therefore clinical promise, are such compounds progressed. But to the credit of the industry – this has been done – for those cases in which the compelling biological activity can be coupled with a means of production. A few such examples are cited below where the supply issue was overcome in order to progress a highly promising MNP.

Hemiasterlins. Wyeth. The lead structure for the development of HTI-286 was the sponge tripeptide hemiasterlin, a microtubule depolymerizing agent that kills cells by causing mitotic arrest, leading to apoptosis. HTI-286 was developed at Wyeth for several oncology indications, based on pioneering work from the laboratory of Professor Raymond J. Andersen at the University of British Columbia. Owing to the peptidic nature of the compound and its amenability to convergent synthesis, the compound was produced on kilogram scale following careful process development at Wyeth.

Discodermolide. Novartis. (+)-Discodermolide, an antitumor polyketide from the Caribbean sponge *Discodermia dissoluta*, was first isolated and characterized in 1990 by Gunasekera. Discodermolide possessed potent antitumor activity as a result of induction of tubulin polymerization and microtubule stabilization. However the compound was available in very limited supply. In a beautiful example of industrial process chemistry, the Novartis group effectively blended elements from the published total syntheses of Amos Smith, Ian Patterson and James Marshall to create an effective synthesis which was used to produce material for clinical trials.

Salinosporamide. Nereus. Salinosporamide A is a novel proteasome inhibitor isolated from the marine actinomycete *Salinispora tropica* by Bill Fenical and co-workers at Scripps Institution of Oceanography. The compound is in clinical development for oncology by Nereus Pharmaceuticals. Owing to the microbial origin of the compound, Nereus has been able to create a highly productive strain of the bacterium, which facilitates the production of the compound.

These three examples illustrate the commitment by small and large pharmaceutical companies to invest in the development of MNPs with highly promising biological activities. The key remains an effective means to solve the supply issue, whether by chemical synthesis, traditional high-yielding fermentation processes or perhaps heterologous expression of pathways in the future."

It is apparent from these opinions from many diverse leaders in the field of MNPs that the potential of MNPs as a major source of new therapeutic entities in the pharmacopeia is still on the horizon. As the major pharmaceutical companies strive to fill their pipelines, the need for sources of diverse and pharmacologically active leads grows ever larger, and natural products both marine and terrestrial still maintain the potential to provide this diversity [53]. The cooperation between academic MNP scientists and those in smaller biotechnology companies will be instrumental to the early preclinical development and mechanism of action studies necessary to provide the compelling preclinical data to generate sufficient interest from larger pharmaceutical companies to support the late preclinical and clinical development of MNPs. This necessitates the need for innovative pharmacology to identify molecular targets for these biologically active MNPs and the ability to synthetically optimize MNP scaffolds to enhance the drug-like properties for development. New technologies, such as marine microbial/fungal genomics, have the potential to elevate MNPs as key sources of new therapeutic entities by solving the key issue of providing sufficient material for development, and provide the potential for identification of very novel MNPs that could not be identified using current laboratory methods.

To sustain the "Renaissance" in MNPs it is apparent that academic researchers must maintain sufficient funding to drive the identification of MNPs with potent biological activity that can be used not only as pharmacological tools to aide in the understanding of biology and disease, but also as potential therapeutic entities against human disease.

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