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The Marine Biodiscovery Pipeline and Ocean Medicines of Tomorrow

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Abstract

Marine organisms possess the capacity to produce a variety of unique and biologically potent natural products for treating human diseases, many of which are currently commercially available or are in advanced clinical trials. Here we provide a short review on progress in the field and discuss a case study of an EU-funded project, PharmaSea, which aims to discover novel products for the treatment of infections, inflammation and neurodegenerative diseases. Research in this sector is opening new doors for harnessing the potential of marine natural products with pharmaceutical properties.

Introduction

A significant portion of the Earth's biodiversity (an estimated 25% of the total number of species on Earth) is comprised of marine species (Mora et al. 2011). These have evolved mechanisms to survive in an extremely different and hostile environment compared to land in terms of light, salinity and pressure. This is reflected by the myriad of secondary metabolites (or natural products) that they produce to defend themselves against predators, to locate mates and to out-compete competitors for limited resources. Many of

these compounds have no terrestrial analogues and are unique in terms of chemical structure and biological activity. What makes these products interesting for humans are their potential applications as pharmaceuticals for the treatment of numerous diseases or as templates for medicinal chemistry.

Humans have been trying to understand and use ocean resources for medicinal purposes since ancient times. The Chinese and Japanese were eating a variety of iodine-rich seaweeds already in 1400 BC that accounted for their low incidence of goitre (Leoutsakos 2004). In Ireland, the red algae *Chondrus crispus* and *Mastocarpus stellatus* were used as a folk cure for colds, sore throats, chest infections and bronchitis for several centuries (Dias et al. 2012). In the early 20th century cod liver oil was an important nutritional supplement in many Northern European countries. However it was only after the 1950s, with the advent of scuba diving and new sampling technologies that scientists began to systematically probe the oceans for useful therapeutics. The number of potential compounds isolated from marine organisms now exceeds 28,000 with hundreds of new compounds being discovered every year (Blunt et al. 2015). However, despite the number of compounds isolated from marine organisms and the biological activities attributed to many of these, those that have either been marketed or are under development are relatively few.

There are several reasons for this including the time and cost it takes to reach the market, difficulties in harvesting the organism, low titres of natural product in producing organisms, difficulties in isolation and purification procedures, problems in obtaining a sustainable supply of the compound, high toxicity of the active compound, ecological impact on natural populations, and insufficient investment by pharmaceutical companies (Torjesen 2015). However, notwithstanding these difficulties there has been a “renaissance” in marine drug discovery in the last decade due to technological developments that have accelerated structural elucidation and screening, and the use of marine microbial genomics to provide biosynthetic pathways for the production of marine natural products (Glasser and Mayer, 2009). The development of emerging “omics” tools such direct sequencing of eDNA, next generation sequencing technologies, metaproteomic and synthetic biology, heterologous expression and bioinformatic tools will improve the discovery and production of these compounds and facilitate the study of biosynthetic pathways of organisms previously inaccessible by traditional methods (see review by Rocha-Martin et al. 2014). This is coupled with the fact that alternate technologies such as combinatorial chemistry have failed to

provide the pharmaceutical industry with the chemical diversity necessary to significantly increase the number of new drug-like leads.

Here we discuss the current state of art of marine compounds approved, developed or in clinical trials for treating various diseases, or marketed as nutraceuticals and cosmeceuticals. Several excellent reviews already exist on marine drug discovery so this paper does not attempt to provide a comprehensive overview, but rather to illustrate some examples of the recent advances in this field. We also discuss the ambitions and efforts of an on-going EU project to find new molecules from microorganisms for the treatment of bacterial and viral infections, and inflammatory and neurodegenerative diseases. With a focus on under-exploited marine phyla of cultivable microorganisms, essentially photo- and chemosynthetic bacteria together with fungi and microalgae, this project aims to achieve optimized and sustainable production of relevant biomass and high added-value compounds for pharmaceutical, nutraceutical and cosmeceutical applications, and to overcome some of the major bottlenecks in the drug discovery pipeline.

Marine Drugs in Clinical Use

Marine-derived compounds are more bioactive than those of terrestrial origin, especially in terms of cytotoxicity. It is no surprise, therefore, that marine natural products have their stronghold in the area of anticancer chemotherapy, as indicated by the list of compounds that have already made it to the market or are currently under clinical investigation. To date, the global marine pharmaceutical pipeline consists of 7 approved pharmaceuticals in clinical use, 4 of which are anticancer drugs (Fig. 1). The first marine-derived anticancer agent to be developed for clinical use, cytarabine or Ara-C, is a synthetic analogue of a C-nucleoside from the Caribbean sponge, *Cryptothethya crypta*, approved in 1969 and still in use today to treat acute myelocytic leukemia and non-Hodgkin's lymphoma (Sagar et al. 2010). Almost 20 years later in 2007 the next anticancer agent from the tunicate *Ecteinascidia turbinata* would be approved, trabectedin (Yondelis), for the treatment of soft tissue sarcomas and ovarian cancer (Schoffski et al. 2008). A third marine anticancer success story was the discovery of the polyether metabolite halichondrin A from the sponge *Halichondria okadai* (Hirata and Uemura, 1986). A simpler structure containing the pharmacophore obtained synthetically gave rise to Eribulin (Halaven), the most complex

synthetic drug ever made, approved for the treatment of drug refractory breast cancer in 2010 (Menis and Twelves, 2011). The most recently approved anticancer compound from the marine environment is brentuximab vedotin (Adcetris), a chimeric antibody attached through a protease-cleavable linker to a derivative of the potent antitubulin agent dolastatin 10 (Katz et al. 2011) used for the treatment of Hodgkin's lymphoma and anaplastic large cell lymphoma.

Marine natural products have also found applications as antiviral drugs used to treat herpes simplex infections. Vidarabine or Ara-A is a synthetic analogue of spongouridine with improved antiviral activity, originally isolated in 1950 from the sponge *Tethya crypta* (Sagar et al. 2010), but currently obtained from fermentation cultures of the bacterium *Streptomyces antibioticus*. Another important marine natural product, ziconotide (commercial name Prialt, Klotz 2006), is a synthetic calcium-channel binding conotoxin from *Conus magus*, the Magician's cone snail, which has proved effective in patients with intractable severe pain who either do not respond to or cannot tolerate other drugs. Additional conotoxins are in clinical development with potential applications in pain management and are widely employed tool compounds in neurotoxin research (Daly and Craik, 2011). Finally, marine products obtained from fish oils, typically from oily fish such as mackerel and anchovy, have found applications as a lipid-regulating agent (commercial name Lovaza) to reduce severe elevations of triglycerides associated with conditions such as obesity, insulin resistance, diabetes mellitus and other factors that contribute to the risk of atherosclerosis or hardening of the arteries responsible for coronary artery disease. According to Gerwick and Moore (2012) the current success rate of discovery from the marine world, namely seven clinically useful and approved drugs from 28,175 discovered molecular entities (e.g. 1 drug per 4,025 natural products described) is approximately 1.2- to 2.5-fold better than the industry average (1 in 5,000–10,000 tested compounds) (http:// www.pharma.org/sites/default/files/159/rd_brochure_022307. pdf).

New Drugs in Development

Currently there are about 26 natural products in Phase I to Phase III clinical trials, 23 as anticancer cancer agents, two for schizophrenia and Alzheimer's, and one for chronic pain

(http://marinepharmacology.midwestern.edu/clinPipeline.htm). Thus, the pipeline of promising marine derived compounds is very strong, and several of these agents are likely to reach the market in the coming years (Mayer et al. 2010). Some of these new marine drugs are discussed briefly in the next section.

Anticancer

Aplidine (dehydrodidemnin B), a depsipeptide dehydrodidemnin isolated from the Mediterranean tunicate *Aplidium albicans* has antiproliferative activity by blocking the cell cycle and inducing apoptosis, with strong activity against multiple myeloma cells. PharmaMar is currently developing Aplidin for the treatment of multiple myeloma (phase III of clinical trials), and for solid and hematological malignant neoplasias, like T-cell lymphoma (phase II of clinical trials) (http://www.pharmamar.com/aplidin.aspx).

Plinabulin is a synthetic analog of a natural product isolated from a marine fungus (*Aspergillus* sp.) that inhibits tubulin polymerization, leading to the disruption of the vascular endothelial architecture of the tumor. BeyondSpring Pharmaceuticals is developing plinabulin and has announced the start of phase III clinical trials in patients with non-small cell lung cancer in 2015 (http://www.beyondspringpharma.com/press-release- plinabulin-phase-3-trial/).

Salinosporamide A (Marizomib; Potts et al., 2011) is a novel, potent proteasome inhibitor from the marine actinomycete, *Salinispora tropica,* that induces apoptosis by a caspase-8 dependent mechanism in multiple myeloma and leukemia cells. Currently, combination therapies of salinosporamide A with other drugs are under investigation in phase I clinical trials.

Further examples of anticancer drugs of marine origin in clinical development are discussed by Newman and Cragg (Newman and Cragg, 2014).

Alzheimer Disease

Bryostatin 1, a macrolide lactone isolated from the bryozoan species, *Bugula neritina*, is a potent modulator of protein kinase C that is currently in Phase II clinical trials for the treatment of Alzheimer's disease by Neurotrope Bioscience (http://www.neurotropebioscience.com/). The drug has shown pre-clinical efficacy to not only treat Alzheimer's disease symptoms, but also its underlying causes. Bryostatin was

originally intended for anti-cancer chemotherapy, but was then discovered to potentially arrest Alzheimer's disease (Lorente et al. 2014). Preclinical testing revealed that it reduced the toxic Alzheimer's disease protein amyloid-β and the deposits of amyloid-β called amyloid plaques, restored lost synapses, and protected against the loss of memory functions.

DMXBA, a synthetic analogue of the toxic alkaloid produced by several nemertinean worm species, such as *Paranemertes peregrine* and *Amphiporus lactifloreus*, improves cognition and sensory deficit in several animal models, and has shown neuroprotective effects *in vitro* and *in vivo* (Rangel and Falkenberg 2015). Phase I and II clinical trials showed a significant cognitive improvement in healthy young adults and in schizophrenic patients (Rangel and Falkenberg, 2015). Comentis Inc. is developing the drug for treatment for Alzheimer's disease and schizophrenia (http://comentis.com/).

Analgesics

The guanidine alkaloid **tetrodotoxin** (TTX), a blocker of voltage dependent sodium channels isolated from fish, algae and bacteria, has shown therapeutic efficacy as an analgesic in cancer patients. Two formulations are currently under evaluation in phases II and III of clinical trials by the Canadian WEX Pharmaceuticals Inc.: the first formulation is in phase III, indicated for the treatment of neuropathic pain in cancer patients; the second one is in phase II of clinical trials, for peripheral pain and cancer-related pain (http:// www.wextech.ca/clinical_trials.asp?m=1&s=0&p=0; http://www. clinicaltrials.gov).

Antibacterials

Despite the urgent need for new antibiotics, particularly to tackle the rise of antibiotic-resistant bacteria, new antibiotic development has moved slowly and there are few compounds in the antibiotic development pipeline. This lack of activity reflects market failure as the risk–reward ratio has been considered unattractive for pharmaceutical companies. Mayer et al. (2013) lists 23 antibacterial compounds in preclinical pharmacological research. An interesting example is **Anthracimycin,** a polyketide antibiotic discovered in 2013, derived from marine actinobacteria that has shown significant activity against *Bacillus anthracis*, the bacteria that causes anthrax (Jang et al. 2013).

Marine nutraceuticals and cosmeceuticals

Currently there is also great interest in marine derived products as nutraceuticals and cosmeceuticals because of their beneficial effects on human health. These often have drug-like properties (hence the term –ceutical) and contain active ingredients such as vitamins, phytochemicals, enzymes, antioxidants and essential oils which are finding uses as natural additives in foods, as nutritional supplements including color additives and antioxidants, and as vitamins, oils, and cofactors which enhance general well-being. Compared to high-value pharmaceuticals, these medium-value products have a rapid route to market and many companies have chosen to go along the functional product route as it offers lower risk and a quicker potential return on investment than the high-risk high-reward pharmaceutical market.

The main products of primary interest for marine nutraceuticals include omega-3 fish/algal oil, phospholipids (bound omega 3-fatty acids), micro/macro algal nutrition supplements, fish proteins and peptides, hydrolysates, shellfish chitin, fish collagen, and mineral supplements (Fig. 2). Polyunsaturated ω-3 fatty acids are purported to have a range of beneficial effects including improved heart health and reduced inflammation. Several population studies report that dietary ω-3 fatty acids or fish oil may also reduce the risk of developing breast, colon, or prostate cancer. In addition to the traditional sources of the ω-3-fish oils, krill oil has also become very popular. This oil is different from the traditional fish oils because it contains three active components: ω-3 fatty acids, phospholipids, and the carotenoid astaxanthin, a potent antioxidant. Marine microalgae are also rich in ω-3 oils. Made from various species of microalgae, this new omega-3 oil is reported to contain the same lipid type as fish oil, triglycerides. The advantage in this case is that production from this source is more eco-sustainable and less damaging to the environment than production of fish and krill oils.

Current nutraceutical markets from marine organisms are also focused on chemicals such as carotenoids due to their high market value, projected to reach € 1.27 billion by 2019 (http://www.marketsandmarkets.com/PressReleases/carotenoid.asp). Carotenoids have much potential as food colorants, feed supplements, nutraceuticals, and for cosmetic and pharmaceutical purposes. There are well over 600 known carotenoids, with beta-carotene, alpha-carotene, lutein, zeaxanthin, lycopene, fucoxanthin and astaxanthin being the most

common. Astaxanthin is one of the better known in terms of its status as a "supernutrient," as it is the only one to easily cross the blood-brain barrier and other bio-membranes which makes it more easily absorbed and transported to all tissues and organs in the body. Research suggests that astaxanthin is an optimum ingredient choice for eye protection, skin health, anti-ageing, anti-fatigue, or any condition where protection from free radicals is needed (Fiedor and Burda 2014).

Another carotenoid, fucoxanthin, may play a role in reducing obesity (Gammone and D'Orazio 2015). So far, only animal studies have been conducted but these show that fucoxanthin, found in edible brown seaweed and microalgae such as the diatoms *Phaeodactylum tricornutum* or *Cylindrotheca closterium*, promotes the loss of abdominal fat in obese mice and rats. Although it is not fully understood how fucoxanthin works, it appears to target protein UCP1 that increases the rate at which abdominal fat is burned. Fucoxanthin has also been found in animal studies to decrease insulin and blood glucose levels. Researchers hypothesize that fucoxanthin may have anti-diabetes effects because it stimulates the formation of ω-3 fatty acids which are thought to increase insulin sensitivity, improve triglycerides and reduce LDL ('bad') cholesterol.

Together with the pharmaceutical and nutraceutical industries, the cosmeceutical industry is increasingly turning to the sea in the search for new molecules. One of the most common molecular classes of compounds used in the personal care bioactive ingredients sector is the exopolyssacharides (EPS). Various microorganisms produce EPS, including proteobacteria, cyanobacteria and archaea. Abyssine by Lucas Meyers is an *Alteromonas* ferment extract containing the EPS HYD657, named deepsane, produced and secreted by the strain *Alteromonas macleodii subsp. fijiensis biovar deepsane* (Cambon-Bonavita et al. 2002). Deepsane is commercially available under the name of Abyssine for soothing and reducing irritation of sensitive skin against chemical, mechanical and ultraviolet B aggression (Martins et al. 2014). A ferment of the deep sea hydrothermal vent bacterium *Thermus thermophilus* (Venuceane™ produced by Sederma Cosmetics) is a potent antioxidant that inhibits damage from reactive oxygen species, protects natural defense enzymes, shields from UV damage, and restores barrier lipids.

Resilience is a line of skin care products from the Estée Lauder Company that contains a special extracellular extract from the Caribbean Sea whip (gorgonian) *Pseudopterogorgia elisabethae*. This extract is mainly composed by pseudopterosins, which are potent anti-

inflammatory and analgesic agents that inhibit eicosanoid biosynthesis by inhibition of both phospholipase A2 and 5-lipoxygenase. Additionally, a derivative of a natural pseudopterosin, methopterosin, has completed Phase I and II clinical trials as a wound-healing agent.

Microalgae are the source of some of the most innovative skin-care products today. Some examples include Dermochlorella DG, XCELL-30, Alguronic Acid and Alguard. Dermochlorella DG from CODIF Reserche & Nature (Britany, France) is a *Chlorella* sp. extract containing oligopeptides that increases firmness and skin tone. XCELL-30 from Greensea (Mèze, France) is developed from microalgae endemic to Madagascar, and specifically acts on cellular turnover in the basal layer of the epidermis, thus allowing the preservation of the youthful characteristics of the skin. Alguronic Acid from Algenist (San Francisco, CA, USA) is an undetermined mix of polysaccharides produced by microalgae with significant anti-aging properties, helping to rejuvenate the skin for a more youthful appearance. Alguard is a natural sulfated polysaccharide compound isolated from a single red microalga (*Porphyridium* sp.) that protects against photo damaging, ageing and micro-abrasion of the skin.

PharmaSea: A case study of a drug discovery project

Marine natural products constitute a strategic research area with potentially enormous economic and social revenues. According to EuroOcean http://www.eurocean.org/np4/2502.html there are over 590 European marine projects that have been funded under both FP6 and FP7 programs (see also Martins et al. 2014), which shows the engagement of academia and industry in bringing more marine bioactives into the market.

An example is the EU PharmaSea project, an SME-academia-driven project initiated by 24 partners in 2012 to discover novel products for the treatment of bacterial infections, inflammation and neurodegenerative conditions such as Alzheimer's disease . The novelty of the project is that it searches for new microbial biodiversity to treat these diseases in some of the deepest, coldest and hottest places on the planet. By choosing deep and cold marine environments scientists hope to tap novel diversity not seen before. Deep ocean trenches are islands of diversity in which evolution may have progressed differently. The work on microorganisms from deep trenches shows they are indeed different. The chemistry derived

from these, though limited in scope, shows high novelty.

Why study these diseases? In the case of antibiotics, the pipeline for new antibiotics has paradoxically experienced a long-term decline. Antibiotics are being developed, but not ones targeting the most urgent needs, and not in the diverse portfolio required to combat the rise of bacterial resistance. No new class of antibiotics has been discovered since 1987 but a new infection emerges on an almost yearly basis (Bérdy, 2012). Diseases such as MRSA have become major problems in hospitals, evolving to become resistant to the limited number of antibiotics available. Hence the urgent need to discover new antimicrobials in many EU drug discovery projects (e.g. MicoB3, MACUMBA and others).

PharmaSea is also looking for compounds targeting inflammatory disorders that underlie a vast variety of human diseases including cancer, atherosclerosis, and Alzheimer's. An estimated 44 million people worldwide suffer from dementia and Alzheimer's disease is the biggest cause, but the treatments available are inadequate only improving some of the symptoms. Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's, affecting approximately 5 million persons worldwide. With the growing and ageing population worldwide, and without the effective cures, it is anticipated that the number of patients with these diseases will increase dramatically in the coming decades. To avert the worst of this crisis, and to secure a sustainable source of more effective drugs, bottlenecks in the drug discovery process must be overcome.

Having its main focus on the discovery of new compounds bioactive in the above mentioned therapeutic areas, PharmaSea also aims to overcome some of the bottlenecks currently found in the biodiscovery process, leading to (1) improvements in the quality of marine resources available for biotechnological exploitation, (2) to shorten time to market, and (3) develop sustainable modes of supply of raw materials for industry. The first challenge is being targeted by exploring the biotechnological potential of microorganisms such as bacteria, fungi and microalgae to overcome problems associated with supply of bioactives since microorganisms are generally more amenable to mass cultivation in large-scale enclosed bioreactors, as already demonstrated for the biofuel and nutritional supplement industries. The two last challenges centre on enabling activities to clarify legal aspects to

facilitate access to marine resources, their sustainable use, and their secure exploitation; and second, to create an improved framework for accessing marine biotechnology data and research materials. To achieve these goals, PharmaSea brings together complementary and world-leading experts, integrating biology, genomics, natural product chemistry, bioactivity testing, industrial bioprocessing, legal aspects, market analysis and knowledge exchange.

Furthermore, to address the issue of inaccessible biodiversity, innovative technologies are being developed to allow more frequent and cost efficient retrieval of, for example, deep-sea microbes. Selection of new habitats such as the deep-sea has increased the number of novel species, which are obtained using selective isolation techniques. Phylogenetic and genomic strategies have further guided selection of strains based on biosynthetic capacity. These high quality strains are being cultured in varying conditions to elicit their biosynthetic repertoire while those recalcitrant to culture are being exploited using a metagenomic approach.

To date the PharmaSea project has cultivated and extracted more than 1400 microbial strains from extreme marine environments, with the majority being fungi and actinobacteria (Figure 3A). These have been cultivated in a number of different media with different stresses applied to elicit production of secondary metabolites. The strains investigated so far have yielded a total of over 15,000 extracts and fractions which have been subjected to a broad range of anti-microbial and central nervous system disease assays (Figure 3B). The pathogenic bacteria and fungi used in this assay panel include gram positive (Methicillin resistant *Staphylococcus aureus,* MRSA) and gram-negative bacteria (*Pseudomonas aeruginosa, Acinetobacter baumannii* and *Escherichia coli*), fungi (*Candida albicans* and *Aspergillus fumigatus*) (Audoin et al., 2013), and two surrogate (avirulent) strains of *Mycobacterium*, namely *Mycobacterium tuberculosis* H37Ra and *Mycobacterium bovis* BCG. Additionally, all samples are also tested in an assay to detect compounds potentiating the effect of the β-lactam antibiotic imipenem against *P. aeruginosa*, with extracts and fractions tested against the pathogen in the presence or absence of a sub-lethal concentration of the antibiotic. Assay incubation times range from overnight in the antibacterial and antifungal assays to 7-day incubations in assays against *Mycobacterium* strains. In order to reduce the high number of hits in anti-infective infective screens (Figure 3C) we are using a state of the art LC/MS based dereplication approach. This immediately excludes extracts containing

known antibiotics and identifies those containing chemical novelty (Lacret et al., 2015). These extracts are being subjected to further work to identify and chemically characterise the active principles.

Neuroactive and psychoactive extracts and fractions for potential applications to treat neurodegenerative disorders such as Alzheimer's and Parkinson's disease, are tested using high-throughput behavioural fingerprinting in zebrafish larvae (e.g. VanHook 2010). Zebrafish-based behavioural fingerprinting provides initial data as to the putative mechanism of action of neuroactive molecules, and provides preliminary mechanism of action information for isolated compounds, thereby helping to rapidly prioritize those with novel mechanisms of action. In addition to anti-infective and neurodegenerative screens, anti-inflammatory and toxicity screens are also carried out (Figure 3C). Figure 3 D further shows the different assays used to evaluate the neuroactivity and anti-inflammatory activity in the primary screen. It also shows the percentage of screening events performed to evaluate toxicity.

Simultaneous with the screening process, extracts are being dereplicated at an early stage through the use of innovative chemometric methods. Extracts identified as validated actives in a selected assay and which are non-toxic have also been evaluated for their likelihood of containing novel compounds using chemometrics. Extracts identified using this protocol are purified using targeted chromatographic techniques followed by pioneering compound dereplication strategies leading directly into an accelerated workflow for full structure determination. This is only possible through the involvement of one of the world's largest chemical databases and a chemical software company, which has enabled the prediction of NMR and MS spectra of most known marine and microbial natural products.

The global aim of PharmaSea is to produce two compounds at larger scale and advance them to preclinical evaluation. Assay cascades are used as the first step in a protocol to decide which extracts to progress. Those showing good in vitro potency, low toxicity and high probability of containing novel compounds are taken forward to isolate the active compounds as potential pharmaceutical candidates. Scale-up fermentation in saline media is being used to generate adequate amounts of target compounds. In addition, identified novel gene clusters are being expressed in heterologous hosts. Extracts that show interesting bioactivity e.g. low cytotoxicity and/or dual activity from cell based screens e.g.

anti-inflammatory & antioxidant, will be subjected to additional screens to identify their potential value as novel applications of marine natural products in personal care and nutrition as part of follow-on projects.

Bioactive compounds will be developed by SME partners and with larger pharmaceutical companies, if appropriate. To address relevant challenges in marine biodiscovery related to policy and legal issues, PharmaSea has brought together practitioners, legal experts, policy advisors/makers and other stakeholders, focusing on the feasibility of harmonising, aligning and complementing current legal frameworks with recommendations and ready to use solutions tailored to marine biodiscovery (Lallier et al. 2014). This work will also generate a toolkit to enable users to explore the existing difficulties of access and benefit sharing under different legal regimes and find practical guidance to secure access to marine genetic resources. Uptake of products derived from marine bioresources will be improved via a number of mechanisms making PharmaSea data/IP available under licence to interested end users.

Concluding remarks

Discovery of natural bioactive molecules is, of course, only the first step in the biodiscovery pipeline. The hardest challenge is turning these products into useful medicines because the costs of bringing a new drug to market from discovery through clinical trials to approval is currently $2,558 million, according to a new study by the Tufts Center for the Study of Drug Development http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study, costs that have more than doubled in the last decade. The same Center also reports that only 11.8 % of drug compounds entering clinical testing are eventually approved. Another major challenge is to reduce the time to market, which is currently circa 10 years. Both factors are discouraging pharmaceutical industries which also have to cope with the fact that the marine environment is largely unexplored and does not offer certainty on the successful outcome of investment. This is complicated by the large investment required to organize oceanographic cruises and to sample in extreme environments where chances of finding greater biodiversity are higher. A further complication regards the legal aspects to access and utilization of marine natural products (or genetic resources) that have been

formalized in a series of agreements such as the Convention on Biological Diversity (CBD) and its Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (Nagoya Protocol, as well as the United Nations Convention on the Law of the Sea (UNCLOS). The Nogoya protocol, expected to enter into force in 2015, will enable stakeholders to better understand and comply with national access and benefit sharing procedures. For example, when the genetic material is accessed from an “ex situ” collection such as a biorepository then the access provision of the CBD and the Nagoya protocol apply. If the genetic material is collected “in situ” during an expedition then UNCLOS provisions will also apply (for further details on legal framework to access and benefit sharing see Lallier et al. 2014 and references therein). Notwithstanding these difficulties, the discovery of new ocean medicines is one of the most promising new directions of marine science today. Novel initiatives including partnering between governmental organizations and industry are being developed to meet the difficulties incurred in the drug discovery pipeline. Projects such as PharmaSea represent an example of such a partnership, as will future programs being organized within the framework of Horizon 2020.

The oceans can therefore provide us with many invaluable benefits and services, including some of the medicines we use to cure human disease. However, the oceans are under serious threat due to pollution and global change. We even contaminate the ocean and its inhabitants by dumping chemicals from drug manufacturing into the world's waterways, polluting villages, cities and aquatic ecosystems around the world, eventually contaminating the fish we eat (Larsson 2014) and the very organisms that could provide us with new cures for human diseases in the future. With the global population projected to increase from seven to nine billion people in the next few decades, there is an urgent need to secure a healthy and productive global ocean. A healthier ocean that is better managed could provide more food and employment. It could also ensure that the benefits from the exploitation of ocean resources can be sustainably managed and equitably shared. Knowledge on the effects of pollution and global change on marine organisms are limited and still relatively unexplored, leaving critical knowledge gaps for those seeking to develop effective policies for sustainable use of marine resources and environmental and human health protection (European Marine Board 2013). A better understanding of the potential health benefits from marine organisms, the compounds they produce, and the

environmental conditions affecting their production will allow for the better management and sustainable development of these valuable marine resources in the future. By pursuing the medical promises hidden within the ocean, while also managing the dangers to human health found in this new frontier, ocean scientists can make a major contribution to improving human health in the twenty-first century and beyond.

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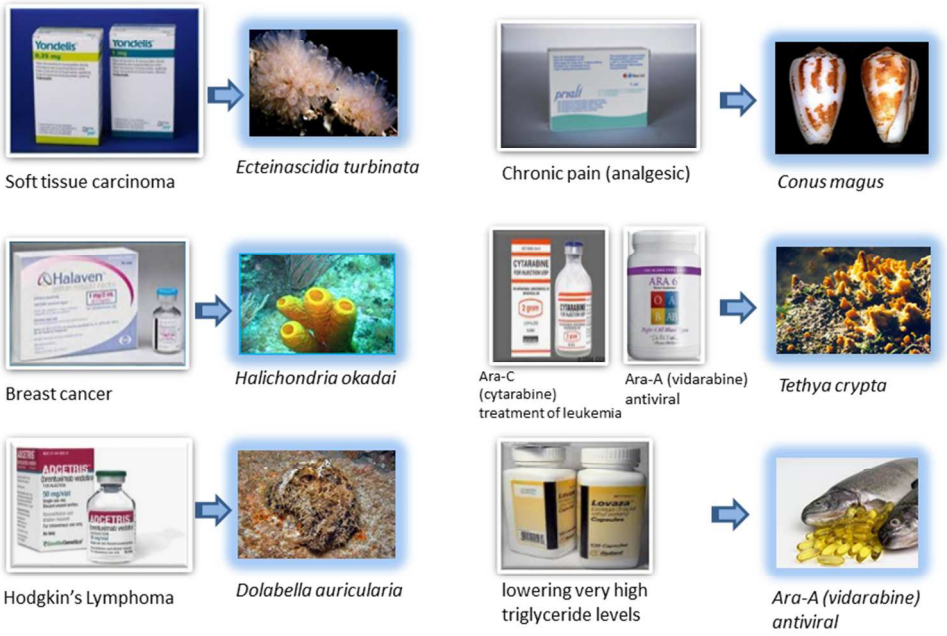
Figure Legends

Figure 1: Pharmaceutical drugs in commercial use.

Figure 2: Marine neutraceuticals and their health benefits.

Figure 3: Pie diagrams showing composition of the PharmaSea strain library (A) and extract library (B) for different groups of microorganisms. Total number of anti-infective (C) and other (D) screening events until June 2015.



Pharmaceutical drugs in commercial use.
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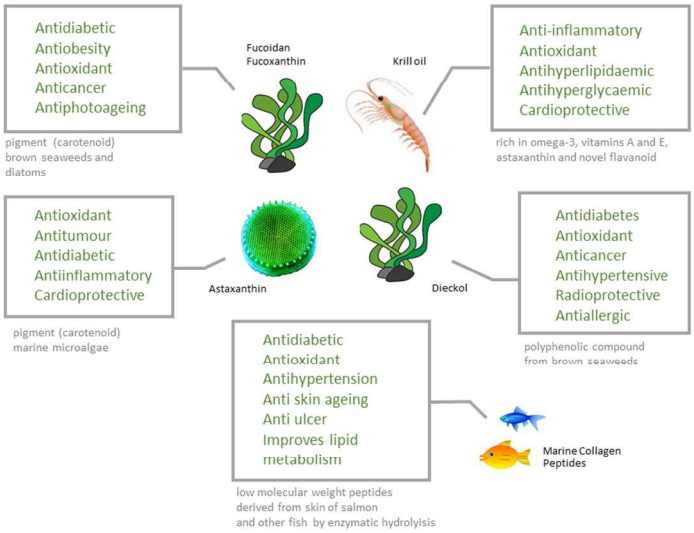
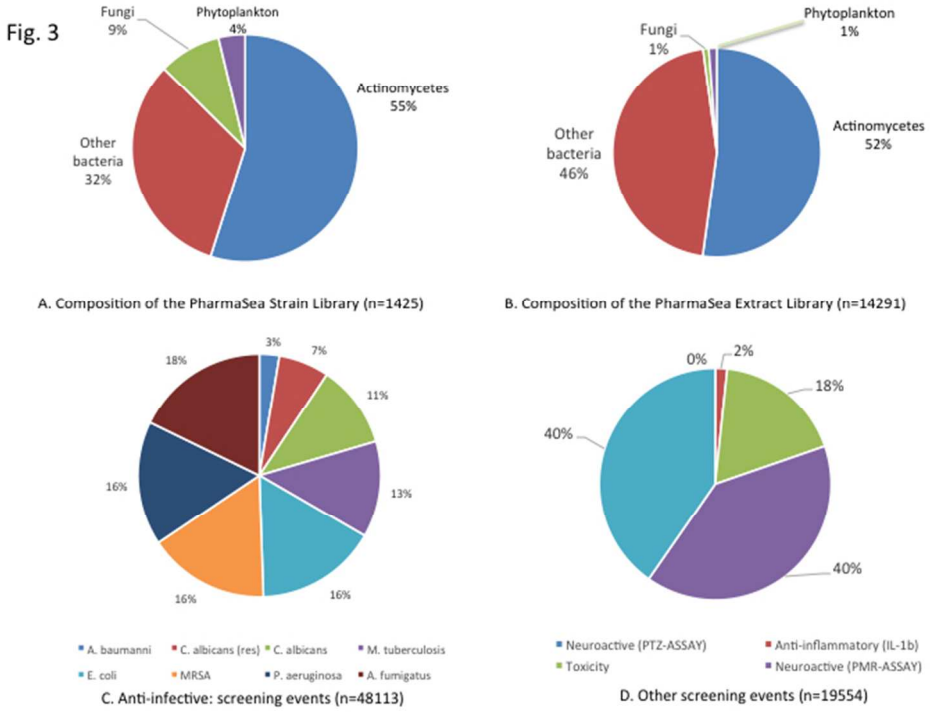


Marine neutraceuticals and their health benefits.
338x190mm (96 x 96 DPI)

Fig. 3



Pie diagrams showing composition of the PharmaSea strain library (A) and extract library (B) for different groups of microorganisms. Total number of anti-infective (C) and other (D) screening events until June 2015.
254x190mm (72 x 72 DPI)