Chapter 3
Current Status and Perspectives in Marine Biodiscovery

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Abstract In recent years the field of marine biodiscovery has experienced profound changes. The initial approach based on the identification of small molecules from marine organisms through processes guided by the search for the targeted bioactivity has led to a number of successes, especially in the field of pharmaceutical research. By contrast, we would like to highlight the benefits of integrating a slightly different approach, mostly based on the construction of chemical libraries and strong collaboration with other fields of marine science including ecology, biology, taxonomy, microbiology, biochemistry, and chemistry in order to better meet the expectations of this approach in a context of sustainability.

3.1 Introduction

During the twentieth century the global population has increased from 1.65 billion to 7.4 billion (http://www.worldometers.info/). The demands of a rising population has resulted in devastating changes to many of the world's ecosystems, the depletion of natural resources and changes to the global climate (http://www.worldwatch.org/). Half of the world's forests have been cleared for human land use and the area of land used for cultivation has increased by approximately 13 % since measurements began in 1961 (www.unep.org).

With the increasing demand for terrestrial ecosystems to be used for cultivation and development, scientists have turned their attention to the exploration of the marine environment for sources of new biomolecules. The advent of SCUBA diving, submersibles, remotely operated vehicles (ROV's) and other technologies, have enabled the sampling of previously unexplored marine habitats. Only a tiny percentage of marine species have been investigated by scientists for diverse applications.

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Many marine organisms have adaptations that enable them to live in habitats which we would consider hostile, such as the high pressure, low temperatures, absence of sunlight and in some cases, low oxygen saturation associated with the deep sea. The opportunity to exploit molecular strategies that have evolved in marine organisms, has had and will have, significant societal benefits. This is exemplified by the green fluorescent protein (GFP) which was first isolated from the bioluminescent hydromedusa *Aequorea victoria* (Shimomura et al. 1962). In 2008 the Nobel Prize in Chemistry was awarded to Osamu Schimomura, Martin Chalfie and Roger Tsien for their discovery and development of GFP, that is now one of the most important tools in cell and molecular research (Phillips 2001).

In addition to these primary biomolecules, a rapid interest has emerged in studying the diversity of small molecules produced by so-called specialized or secondary metabolism. Similar to terrestrial species, marine organisms biosynthesize unique small molecules such as terpenes, steroids, polyketides, peptides, alkaloids and porphyrins. The potential of novelty is huge in this context. In their review of new marine natural products from invertebrates, Leal et al. (2012) reported that of the 11 phyla that have so far been investigated, and which contain approximately 170,000 valid species, less than 1 % of them have been the subject of biodiscovery studies. Many of these compounds are derived from biosynthetic pathways that are uniquely marine (Garson 1993). The marine environment is unlike terrestrial habitats in that it contains an extremely high diversity of sessile invertebrates that rely on bioactive compounds to deter predators, prevent fouling, compete for space or paralyse prey (Paul et al. 2011).

Since the early 1960s, a race commenced involving the random harvesting of marine organism and analysing them for useful biomolecules. This area of research is referred to as ‘marine bioprospecting’. No clear definition was given, but rather a broad concept was embraced involving the collection of organisms from a given region with the aim of identifying those that could be exploited for human use. The Food and Agriculture Organisation workshop on marine bioprospecting suggested that the term bioprospecting should be divided into two terms: ‘biodiscovery’ as the first phase of scientific research into a region’s biodiversity and ‘bioprospecting’ as the second and subsequent phases of re-collection of biological resources for further investigation, with a view to commercial exploitation (http://www.fao.org/docrep/009/a0337e/A0337E15.htm).

Intensive marine bioprospecting began in the early twenty-first century in seas around Australia and New Zealand (Capon 2008) and later spread to all regions of the world, including Ireland (Rae et al. 2013), Scotland and Norway (Svenson 2013). The Biodiscovery Act published in 2004 in Queensland, Australia is without doubt a landmark in the development of this approach. In the same time, Ireland launched a large programme in marine biodiscovery called the Beaufort project (http://www.qub.ac.uk/research-centres/MarineBiodiscovery/). A Marine Biodiscovery Centre was established at Aberdeen, Scotland (http://www.abdn.ac.uk/ncs/departments/chemistry/marine-biodiscovery-centre-112.php) and a research centre in Marine Biotechnology and Biodiscovery by GEOMAR-Biotech at Kiel, Germany (http://www.geomar.de/en/research/fb3/fb3-mn/geomar-biotech/)

was also established. One of the most renowned centres in this area is located at the Scripps Institute of Oceanography, San Diego, USA (https://scripps.ucsd.edu/cmbb).

Due to the novelty of the chemical structures of marine metabolites, the main and most lucrative interest was focused on the search for new medicines (Baker 2015). After some initial screening of marine macro-invertebrates, most of the current research carried out by large consortia around the world is dedicated to the isolation and culture of marine micro-organisms (Jaspars et al. 2016; Reen et al. 2015; Rocha-Martin et al. 2014; Fuerst 2014; Muehling et al. 2013; Kurtboeke 2012; Capon 2012; Joint et al. 2010; Heidelberg et al. 2010). The main justification for using micro-organisms over macro-organisms, is the ability to perform large-scale culture of microbes in the laboratory which enables control over the production of particular compounds. In this context, several pharmaceutical companies, often in collaboration with academic laboratories, have organized expeditions throughout the world's oceans in a search for new drugs. The most striking outcomes of this research culminated in the marketing of several drugs that are used today to treat human diseases. In the first part of this chapter we will detail (a) the successes of this approach, but also (b) some of the limitations that have been identified.

In recent decades there has been a growing awareness of the negative impacts we are having on the environment. Governmental, non-governmental and international organizations have emphasised the need to address the problem of environmental damage caused by uncontrolled economic development. Initially, international legislations permitted the exploitation of resources without the requirement to share benefits with the people living in close vicinity to the natural resources being exploited. The European Environment Agency have identified climate change, pollution, ocean acidification, over-fishing and invasive species as serious threats to marine bioresources and diversity (http://www.eea.europa.eu/highlights/marine-biodiversity-life-in-seas).

It is timely therefore that we consider a new approach to marine biodiscovery that is centred upon a more sensitive and sustainable use of our marine resources. The Nagoya Protocol and the United Nations Convention on the Law of the Sea today provide a legal framework for helping to ensure benefit sharing when a bioresource leaves the country of origin (https://www.cbd.int/abs/text/; http://www.un.org/Depts/los/index.htm). In the second part of this chapter we will propose some perspectives for a more enlightened use of marine bioresources.

3.2 The Bioguided Approach

The main strategy used to identify new compounds of marine origin for cosmetic or pharmaceutical applications is the bioguided screening process (Fig. 3.1). Companies that invest in the marine environment to provide their products and incomes have developed their own screening facilities on specific targets. Expensive expeditions have been organized mostly by companies to investigate the world's oceans and collect a large diversity of marine species (Bhatia and Chugh 2015). However, in the 1990s benefit sharing agreements were not fully in place and the

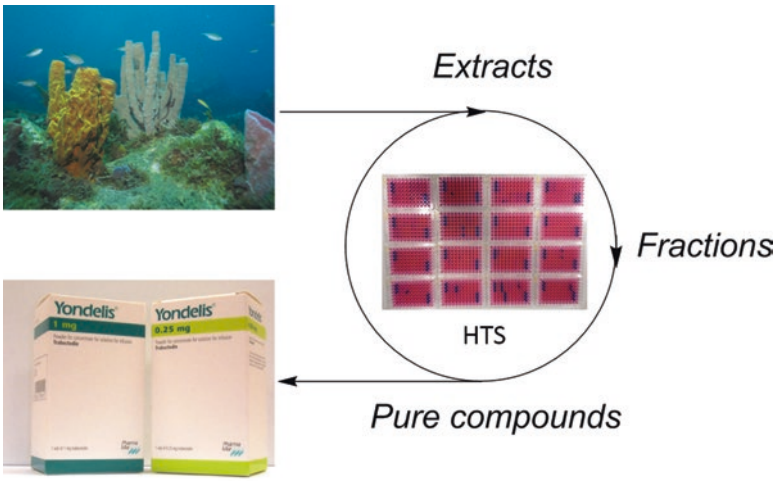

Fig. 3.1 Marine biodiscovery in the context of bioguided and high throughput screening (HTS)

expeditions usually did not involve the participation of the local population or scientists. Collecting permits were granted because the authorities were attracted by putative future benefits. Most of the collections contained a random assortment of marine organisms. Some culture collections of marine samples were then built especially in the laboratories of the companies which financially supported the expeditions (https://www.pharmamar.com/). Whilst some of the academic researchers who were involved in obtaining the original collecting permits were associated with parts of the studies, most if not all of the intellectual property rights remain with the companies that funded the initial collecting expeditions. This wealth is today mostly concentrated in the private sector as the awareness of the economic value was long to be recognized at national levels. In most cases some academic chemists participated in the expeditions and collections, but often marine biologists and specialist taxonomists were not associated with this work, because documenting the biodiversity and species identification were not considered as priorities. Different types of extracts were produced from all kinds of marine organisms, including microbes, algae and a large number of animals, and screened for a specific target after building the culture collection. The screens have focused on anticancer activities, mainly because marine compounds are often more cytotoxic than terrestrial ones, but also because cancers have a major impact on human health. Below we review the major successes in marine biodiscovery, most of which are in the pharmaceutical sector.

3.2.1 Fishes

Omega-3-Acids (Anti-Hypertriglycerimedia): Ethyl esters of omega-3-acids, isolated mainly from fish oils are used as anti-hypertriglyceridemic drugs (Fig. 3.2). Lovaza® is the formulation which chiefly contains the ethyl esters of

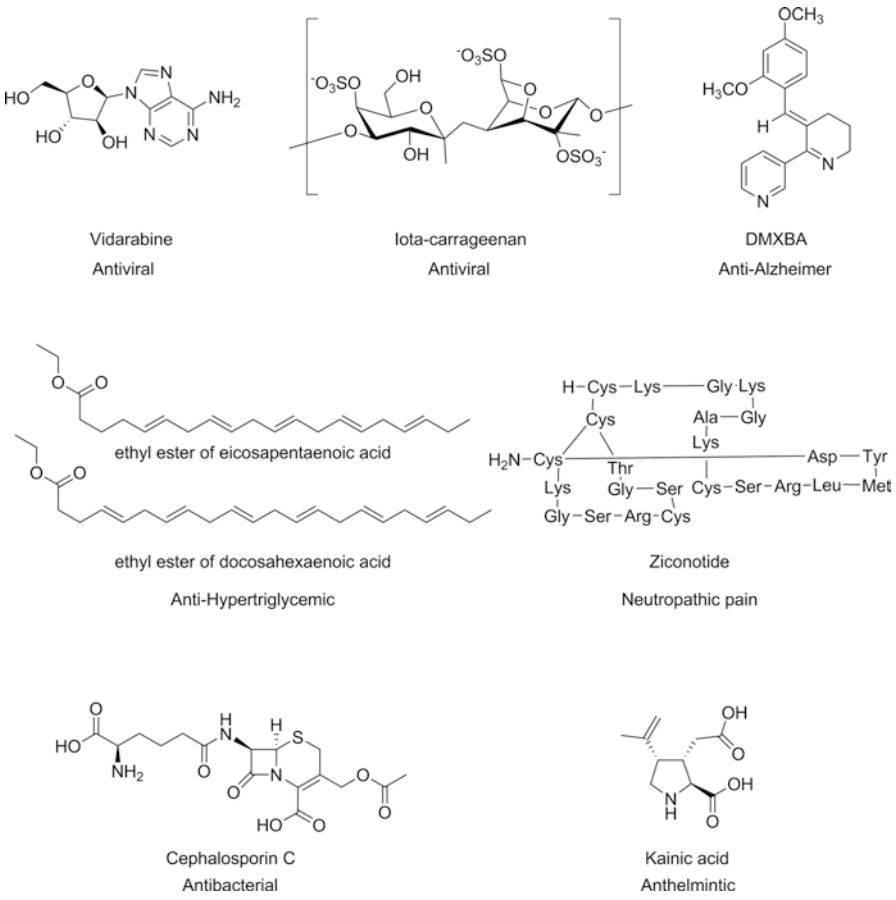

Fig. 3.2 Marine natural products with applications (except anticancer)

eicosapentaenoic acid and docosahexaenoic acid, along with other omega fatty acids esters. They are proven to reduce triglycerides and low density cholesterols and to increase high density cholesterols in the blood. They are used therapeutically, along with other statins and/dietary supplements, to lower triglycerides levels (Davidson et al. 2012; Koski 2008; Lovaza: GlaxoSmithKline 2014)

3.2.2 Porifera

Tethya Crypta

Cytarabine (Cytosar-U®): Cytarabine (Ara-C) is the first marine anticancer molecule and was discovered in 1945 by Werner Bergmann (Fig. 3.3). This active small molecule is a nucleoside isolated from the Caribbean sponge *Tethya crypta* (Newman et al. 2009) and is used for the treatment of leukemia. Intracellularly it is converted

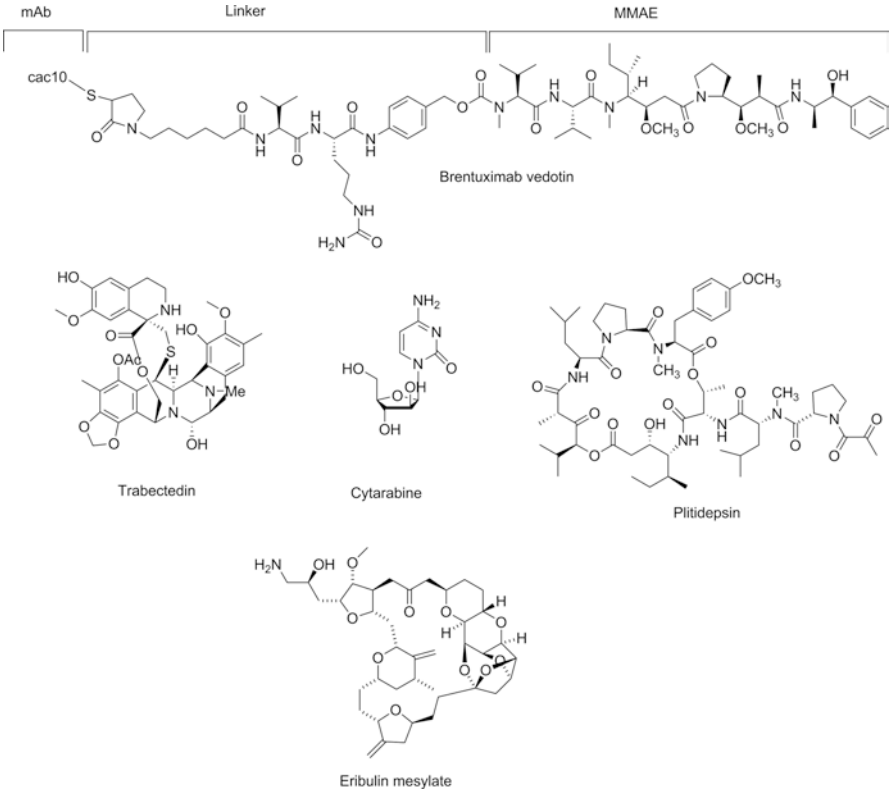

Fig. 3.3 Marine natural products as anticancer/antitumoral agents

into cytosine arabinoside triphosphate that acts as a cytotoxic agent inhibiting DNA polymerase and DNA synthesis (Mayer et al. 2010). Due to its discovery being 70 years ago, extensive studies and trials have been conducted and the drug has been in use for over 40 years. Cytarabine is a simple molecule with similarity to RNA bases.

Tethya Crypta **and** *Streptomyces Antibioticus* **(Actinobacteria)**
Vidarabine (Fig. 3.2) (Antiviral): Vidarabine (Ara-A) is a synthetic antiviral purine nucleoside derived from the natural product spongouridine. Currently obtained from *Streptomyces antibioticus*, it was isolated initially from the Caribbean sponge *Tethya crypta.* Being structurally similar to adenine, it functions as an antimetabolite. After being metabolically converted into its triphosphate form, it inhibits viral DNA polymerase and thus DNA synthesis. Vidarabine was approved by FDA in 1976. However due to its lower therapeutic window in comparison to other antiviral drugs in the market, it was discontinued in the USA in June 2001. Ophthalmic ointment is still in use in the EU against acute keratoconjunctivitis and recurrent epithelial keratitis. It is useful against rhabdoviruses, hepadnarviruses, herpes virus, poxvirus and shingles (Hayden and Douglas 1995; De Clercq 1993; Chabner and Glass 1996; Schabel Jr 1968).

Halichondria Okadai
Eribulin mesylate (Fig. 3.3) (Halaven®): Eribulin mesylate is a marine derived microtubule-targeted agent that was approved in 2010 for use against metastatic breast cancer in patients who have already undergone chemotherapy (Huyck et al. 2011). It is a structurally simplified synthetic analogue of halichondrin B which was originally isolated from the marine sponge *Halichondria okadai* (Dumontet and Jordan 2010). As there was a limited supply of the natural source, there was a clear need for a synthetic analogue. Simplified analogues were discovered, which included eribulin, while searching for the best synthetic route toward halichondrin B. Eribulin inhibits the growth of microtubules hence leading to G2/M cell cycle arrest and ultimately apoptotic cell death.

3.2.3 Chordata, Tunicata

Ecteinascidia Turbinata
Trabectedin (Fig. 3.3) (Yondelis®): Trabectedin was approved by the European Commission in 2007 for the treatment of patients with soft tissue sarcoma (SAS) and in 2009 for treatment of ovarian cancer. In the USA the drug was approved only in 2015 for treatment of SAS. Trabectedin is only advised to be used if previous chemotherapy has failed since severe, negative effects on human health are possible (D'Incalci and Galmarini 2010). The compound is an alkaloid isolated from the tunicate *Ecteinascidia turbinata*. Its chemical structure allows the molecule to bind to DNA *via* two tetrahydroisoquinoline rings, while the third ring is proposed to protrude and interact with DNA binding proteins. It is known that trabectedin also affects transcription factors and DNA repair pathways.

PM01183 (Fig. 3.4): This is another synthetic analogue of ecteinascidins, a potent antitumor compounds isolated from the tunicate *Ecteinascidia turbinata* (Rinehart et al. 1990). Two fused tetrahydroisoquinoline rings of PM01183 play a role of recognition and binding to DNA of tumor cells, while a tetrahydro-β-carboline protrudes from the DNA groove ultimately causing DNA damage *via* double strand breaks. This alkaloid is used for treatment of solid tumours and is currently being used in Phase II clinical trials.

Aplidium Albicans
Plitidepsin (Fig. 3.3) (Aplidin®): this highly potent depsipeptide plitidespin was isolated from the Mediterranean tunicate *Aplidium albicans* but is produced currently through synthesis by the Spanish company Pharmamar (Mayer et al. 2010). Plitidepsin is active against multiple myeloma. The drug causes apoptosis and inhibition of protein synthesis and acts as an angiogenesis inhibitor. Current clinical trials are promising and indicate that whether alone, or in combination with other active agents, plitidepsin will be useful in combating multiple myeloma (Mitsiades et al. 2008). At the chemical level, plitidepsin is a macrocycle that is constituted of 6 subunits and one side chain.

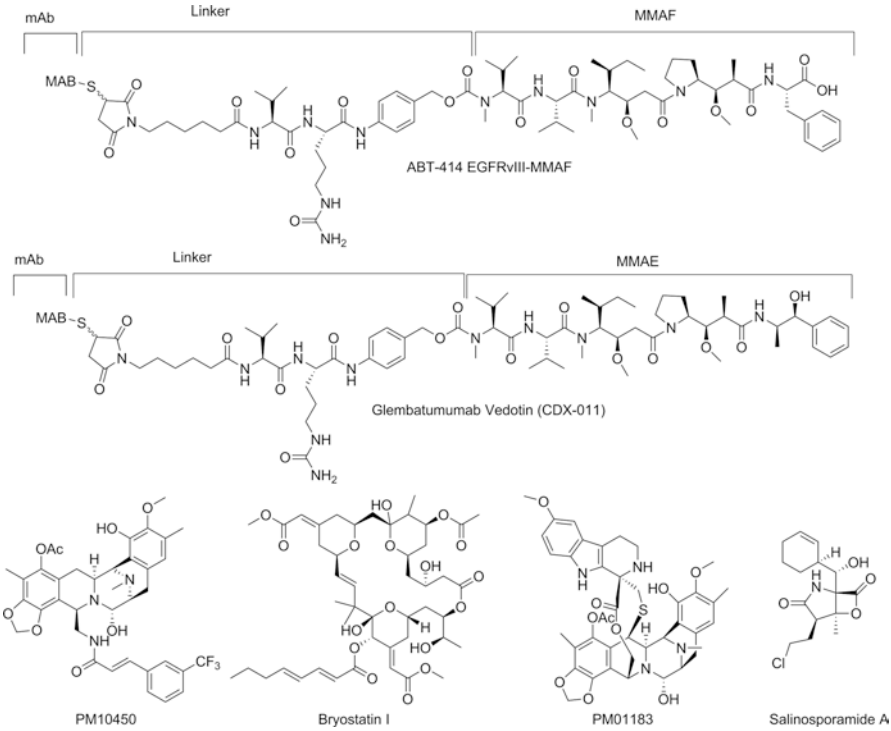

Fig. 3.4 Additional marine natural products as anticancer/antitumoral agents

3.2.4 Bryozoa

Bugula Neritina

Bryostatin: Bryostatin-1 (Fig. 3.4) is a macrocyclic lactone with antineoplastic activity isolated from a marine invertebrate bryozoan *Bugula neritina*. The main mechanism of action is modulation of the regulatory domain of protein kinase C. Transient contact to bryostatin-1 promotes activation of PKC, whereas long-lasting exposure advances huge down regulation of PKC. In various haematological and solid tumor cell lines, bryostatin-1 restrains multiplication, impels separation, and advances apoptosis. Stage I studies recommended noteworthy antineoplastic action against a few types of tumor and defined the main dose-limiting toxicity as myalgia. Bryostatin-1 has later been examined broadly in stage II clinical trials as a single agent in patients with malignancies including lymphoma, leukaemia, and melanoma. Although there is nominal single-agent activity, combination chemotherapy with standard medications is giving exceptionally reassuring results and indicates a new direction in cancer therapy. The major toxicities are myalgias, nausea, and vomiting.

However, because of practical difficulty in harvesting it from the naturally occurring bryozoan, and long chemical syntheses that were too cumbersome for drug makers,

the compound has fallen out of favor as drug candidates. Recently, the cloud that was hanging over the bryostatins has begun to lift. Animal tests show that bryostatin 1 augments memory and could be used to treat Alzheimer's disease and strokes, and some preliminary studies show it could help eliminate HIV. Based upon a number of Blanchette Rockefeller Neurosciences Institute (BRNI) pre-clinical and autopsy-validated human tissue studies, PKCε deficits have been implicated as a potential cause of Alzheimer's disease.

Neurotrope Bioscience has an exclusive license to develop and commercialize bryostatin for cognitive disorders. The Company is approaching the treatment of Alzheimer's disease through the activation of PKCε. Bryostatin is a potent modulator of an enzyme protein kinase C, epsilon (PKCε). Activation of PKCε isozymes improves learning and memory by (a) inducing synthesis of proteins required for long-term memory, (b) increasing brain neurotropic factors, (c) reducing neurotoxic amyloid accumulation and tau protein hyperphosphorylation and (d) inducing synaptogenesis. Currently Neurotrope Bioscience is conducting Phase II clinical trials on bryostatin for Alzheimer's disease (Pettit et al. 1982; Kraft et al. 1986; Berkow and Kraft 1985; Kortmansky and Schwartz 2003).

3.2.5 Mollusca

Conus Magnus
Ziconotide (Fig. 3.2) (Prialt®, Neutropathic pain): This is a synthetic form of ω-conotoxin, a toxin isolated from the cone snail *Conus magus*. It was made by solid phase synthesis in 1987 and was approved by FDA in 2004 and EMEA in 2005. It acts by blocking *N*-type voltage-sensitive calcium-channels at neuromuscular junctions and thus inhibits the release of pro-nociceptive chemicals. After morphine, ziconotide was the first intrathecal analgesic drug to be approved. However, because of the invasive procedure involved, it is only recommended for the management of severe chronic pain, which otherwise cannot be managed by orally available analgesics. It is preferred over morphine, because of non-opioid related side effects. However its low dose titration, in combination with opioid based therapy, is recommended for neuropathic pain in cancer patients (de la Calle Gil et al. 2015; Staats et al. 2004; Atanassoff et al. 2000).

Jorunna Funebris **and** *Neopetrosia* **sp. (Porifera)**
PM10450 (Zalypsis®): PM10450 (Fig. 3.4) is a synthetic derivative produced by Pharmamar and derived from the original alkaloids Jorumycin and Renieramycin J, isolated from the nudibranch *Jorunna funebris* and the sponge *Neopetrosia* sp. respectively (Petek and Jones 2014). Like plitidepsin, zalypsis acts against multiple myeloma by causing cell cycle arrest, apoptosis and DNA double stranded breaks. The IC_{50} values of the antimyeloma agent zalypsis are outstanding – within the picomolar or low nanomolar range. Moreover, zaplypsis showed activity against resistant cells, which means that the drug can potentially be used for patients already treated for multiple myeloma.

Dolabella Auricularia **and** *Symploca* **sp. (Cyanobacteria)**

Brentuximab vedotin (Adcetris®): Brentuximab vedotin is an anticancer agent that originated from the highly potent dolastatin 10 molecule. Dolastatin 10 (Fig. 3.3) was first isolated from the sea hare *Dolabella auricularia* (Pettit et al. 1987). Subsequently, the cyanobacteria *Symploca* sp. was identified as the true source of the molecule (Luesch et al. 2001). This compound found in this mollusk/cyanobacterium complex has led to a large diversity of drugs in preclinical or clinical trials. Due to a high interest in dolastatin 10, several analogues were synthesized including molecules of the class auristatin (Pettit et al. 1998). Dolastatin 10 entered into Phase II clinical trials, but due to a very high toxicity it was substituted by the synthetic analogue – monomethyl auristatin E (MMAE) coupled to a monoclonal antibody (mAb) (Perez et al. 2005). The concept of Antibody Drug Conjugate (ADC) (Senter and Sievers 2012) is one of a drug composed of coupled cytotoxic molecules to tumor-selective antibodies *via* a linker. ADCs are highly selective due to tumor-seeking antibodies that preferentially bind to tumor cells over normal cell. The antibody used in this particular ADC is the one targeting CD30, which is an antigen highly expressed in Hodgkin lymphoma cells. The linker used with this ADC is valine-citrulline (Val-Cit) dipeptide linker that releases MMAE after proteolysis. Brentuximab vedotin was approved quickly and is currently in the market for treatment of Hodgkin lymphoma.

ABT-414 EGFRvIII-MMAF: ABT 414 is an ADC that links the anti-Epidermal Growth Factor Receptor (EGFR) antibody ABT-806 to monomethylaurisatin F (MMAF) *via* a linker (Fig. 3.4) (Reilly et al. 2016). MMAF conjugate is as much a potent antimitotic agent as MMAE, described previously, but the main difference between them is the presence of phenylalanine at the C-terminus of MMAF. ABT 414 is designed in such way that it binds to cancer cells that are overexpressing EGFRde2-7 (EGFRvIII) and EGFR, causing major recovery even in the most difficult cases. Moreover it is possible to use this ADC in conjugation with radiation and temozolomide treatment causing significant positive effects in glioblastoma models.

Glembatumumab Vedotin (CDX-011): Glembatumumab Vedotin is an ADC that includes in its structure the glycoprotein nonmetastatic B (GPNMB) mAb linked to MMAE (Fig. 3.4) (Vahdat and Chan 2015). In fact GPNMB is an attractive target because it is overexpressed in 85 % of patients with metastatic melanoma including triple-negative breast cancer that is particularly challenging to treat. Glembatumumab vedotin is currently under development by Celldex therapeutics for treatment of metastatic breast cancer and stage III and IV melanoma.

PSMA-ADC: Prostate-specific membrane antigen (PSMA)-ADC is a drug that consists of fully human PSMA mAb linked to MMAE *via* a valine-citrulline dipeptide linker (Ma et al. 2006). ADC is highly specific since PSMA is a typical cell surface marker of prostate cancer (Davis et al. 2005). The company responsible for the production and development is Progenics Pharmaceuticals (Tarrytown, NY, USA), and the drug is currently in Phase II of clinical trials.

GSK2857916: GSK2857916 is constituted by an antagonistic anti-B-cell maturation antigen (BCMA) mAb linked to MMAF *via* a non-cleavable linker (Tai et al.

2014). In this particular ADC, the mAb was afucosylated, which improved the binding affinity of ADC towards BCMA overexpressed in multiple myeloma cells. GSK2857916 causes G2/M cell cycle arrest and apoptosis, the effect of which is enhanced by the ability of the drug to (a) cause multiple myeloma cell lyses, (b) eliminate these vastly distributed cells and (c) initiate their macrophage-mediated phagocytosis. The drug is currently under development by GlaxoSmithKline (GSK), Brentford, UK.

DNIB0600A: This ADC consists of a IgG1 anti-multi-transmembrane, sodium-dependent phosphate transporter (NaPi2b) mAb linked to MMAE through an undisclosed linker (Burris et al. 2014). Currently Phase I and Phase II trials are on-going on patients with non-small cell lung cancer, platinum resistant ovarian cancer and others. Genentech/Roche (San Francisco, CA, USA) produces DNIB0600A.

Pinatuzumab vedotin (DCDT-2980S): Pinatuzumab vedotin is another ADC that is composed of humanized anti-CD22 IgG1 mAb connected to MMAE through maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl linker (Li et al. 2013). CD22 is an attractive target since this antigen is overexpressed solely in B cells and non-Hodgkin lymphomas. *In vitro* and *in vivo* studies showed tumor regressions in mouse and cynomolgus monkey models. Current development and production is by Genentech/Roche (San Francisco, CA, USA).

Polatuzumab vedotin (DCDS-4501A): this ADC is produced by Genentech. Its structure is composed of the antimitotic MMAE coupled to anti-CD79b mAb (Health 2016b). Polatuzumab vedotin exhibits a selectivity towards the transmembrane protein CD79b expressed on B cell lymphoma. Upon binding to CD79B, the linker connecting mAb and MMAE ceases through a proteolytic cleavage and MMAE causes G2/M cell cycle arrest and apoptosis through tubulin polymerization. This particular drug is in Phase II clinical trials as an alternative to pinatuzumab vedotin for treatment of follicular B cell lymphoma and Phase I trials against different types of lymphomas.

AGS-16C3F: AGS-16C3F is an ADC that includes in its structure AGS-16C, a human IgG2k mAb specific to ectonucleotide pyrophosphatase/phosphodiesterase family member 3 (ENPP3), attached to MMAF *via* a maleimido-caproyl linker (Newman and Cragg 2014). This drug specifically binds with high affinity to AGS-16 that is overexpressed in renal and liver carcinoma, after which the MMAF is released via proteolytic cleavage of the linker. MMAF then acts by inhibition of tubulin polymerization that causes G2/M cell cycle arrest and apoptosis (Health 2016a). The drug is currently produced by Agensys & Astellas Pharma (Northbrook, IL, USA) and the phase I clinical trials are ongoing.

AGS-67E: AGS-67E is an ADC that consists of the human IgG2 anti-CD37 antibody attached to MMAE *via* a maleimidocaproyl – valine – citrulline – p – aminobenzyloxycarbonyl linker (Pereira et al. 2015). CD-37 is a tetraspanin transmembrane protein overexpressed on B cells. It is involved (a) in the role of a death receptor (Lapalombella et al. 2012), (b) possibly in the regulation of B/T-cell interaction and proliferation and (c) in immune responses (van Spriel et al. 2004; Knobeloch et al. 2000). AGS-67E exhibited highly potent activity against several non-Hodgkin lym-

phoma and chronic lymphocytic leukemia cell lines *via* apoptosis events and cell-cycle alternations. Current development is conducted by Agensys & Astellas Pharma (Northbrook, IL, USA).

ASG-15ME: this particular ADC was developed for treatment of advanced urothelial cancer (Morrison et al. 2016). The drug is constituted by the human gamma 2 antibody (Igγ2) coupled to MMAE *via* a protease-cleavable linker. The mAb is directed to SLITRK6, the overexpressed antigen in bladder tumor cells. The *in vitro* and *in vivo* studies by Morrison et al. (2016) revealed excellent anti-tumor activity of ASG-15ME against bladder and lung models (Morrison et al. 2016); it is produced by Seattle Genetics (Bothell, WA, USA).

ENFORTUMAB VEDOTIN: ENFORTUMAB VEDOTIN (ASG-22ME, formerly AGS-22M6E) is an ADC sourced under a Phase 1 clinical trial supported by Astellas Pharma Inc and Seattle Genetics Inc. ASG-22ME contains a human monoclonal antibody, AGS-22 focusing on the cell adhesion molecule nectin-4 which is a tumor related antigen, and is over expressed in variety of cancers including breast, bladder, lung and pancreatic malignancy. The antibody is conjugated to the engineered cytotoxic agent MMAE, by means of an exclusive catalyst cleavable linker (AGS-22CE, Seattle Genetics' proprietary innovation), with potential antineoplastic activity. The monoclonal counter-acting agent moiety of AGS-22CE specifically ties to nectin-4. After internalization and proteolytic cleavage, MMAE ties to tubulin and hinders its polymerization, which brings about G2/M stage capture and instigates apoptosis in nectin-4 over communicating tumor cells. The linker framework is intended to be steady in the circulatory system and discharges the cell-killing specialists once inside target malignancy cells. This methodology is expected to diminish considerably much of the poisonous impacts patients might encounter amid treatment with customary chemotherapy while improving the antitumor activity. Currently, ASG-22ME is in a phase 1 clinical trial to evaluate the safety and antitumor activity of increasing doses of ASG-22ME in patients with solid tumors (Perez et al. 2014; Roberts et al. 2013; Trail 2013).

DEDN6526A: DEDN6526A is an antibody–drug conjugate (ADC) sourced from the same mollusk/cyanobacterium complex and under Phase – 1 clinical trial supported by Genentech Inc/Roche Inc. In preclinical studies, DEDN6526A confirmed dose-dependent antitumor activity in ETBR-expressing tumor xenografts. The preparation comprises the antimitotic agent MMAE combined to humanized immunoglobulin G1 anti-endothelin B receptor (ETBR) monoclonal antibody via a protease labile linker. ETBR is a G-protein-coupled receptor that can activate RAF/MEK signaling, and is over expressed in more than 50 % of metastatic melanomas. It is allied with malignant conversion of melanocytes and with potentiation of metastatic spread, which could explain its role in the development of melanoma. Clinical benefits were observed starting at a dose of 1.8 mg/kg and the most common adverse events were fatigue, chills, diarrhea, alopecia, nausea, headache, decreased appetite, infusion-related reaction, peripheral sensory neuropathy, asthenia, and vomiting. The drug is predicted to be a potent option for monotherapy and also viable for combinational chemotherapy (Infante et al. 2014).

DMUC5754A: DEDN6526A or Sofituzumab Vedotin is an Antibody–drug conjugate (ADC) under Phase – 1 clinical trial supported by Genentech Inc/Roche Inc.

In preclinical cancer studies, DMUC5754A established selective targeting of MUC16 and antitumor activity. DMUC5754A consists of a humanized monoclonal antibody against MUC16, a transmembrane glycoprotein that is over expressed in ovarian cancers, linked via labile linker to monomethyl auristatin (MMAE), a potent anti-mitotic drug that inhibits cancer cells' ability to form microtubules. When the drug binds to MUC16, a linker molecule releases MMAE into the cancer cell and destroys it. Clinical pharmacokinetic results from phase -1 study in patients with advanced, recurrent, platinum-resistant ovarian cancer confirmed that 2.4-mg/kg dose is the potentially clinical relevant dose with fatigue nausea, vomiting, decreased appetite, diarrhoea, and peripheral neuropathy as side effects. These results are promising and viable representing a novel type of therapy for ovarian cancer, with effectiveness in platinum-resistant ovarian cancer, which is the hardest type of ovarian cancer to treat (Liu et al. 2013; Wang et al. 2015; Weekes et al. 2016).

DSTP3086S: DSTP3086S, or Vandortuzumab vedotin, is an Antibody–drug conjugate (ADC) under Phase – 1 clinical trial supported by Genentech Inc/Roche Inc. DSTP3086S is composed of a humanized IgG1 mAb against Six Transmembrane Epithelial Antigen of the Prostate (STEAP1), linked *via* a protease-cleavable peptide linker to MMAE. It is a potent anti-mitotic drug that inhibits cancer cells' ability to form microtubules. A phase -1 trial demonstrated an acceptable safety and tolerability profile with minimal adverse side effects. Anti-tumor activity was detected in prostate cancer with acceptable pharmacokinetics that was linear and predictable. With these promising results DSTP3086S is expected to be a viable option to treat metastatic castration-resistant prostate cancer (Danila et al. 2013).

HuMax-CD74: HuMax-CD74 is an ADC under Phase 1 clinical trials supported by GenMab in collaboration with Seattle Genetics Inc. This compound is combined with MMAE, a potent anti-mitotic drug that inhibits the ability of cancer cells to form microtubules. This ADC uses HuMax-CD74, an antibody that targets the HLA class II histocompatibility antigen gamma chain (CD74), which is expressed on a wide range of haematological malignancies and solid tumors. The selective targeting of cancer cell approach by HuMax-CD74 is expected to establish new trends in treatment options for ovary, cervix, endometrium, bladder, prostate head and neck cancers (Van Berkel et al. 2012).

Indusatumab vedotin: MLN-0264 (Indusatumab vedotin) is an Antibody–drug conjugate (ADC) under Phase – 1 clinical trial supported by Takeda/Millennium Pharmaceuticals in collaboration with Seattle Genetics Inc. MLN-0264 contains a monoclonal antibody directed against guanylyl cyclase C (GCC or GUCY2C), a transmembrane receptor normally found on intestinal cells and dopamine neurons in the brain. It is also over expressed on the surface of gastrointestinal cancers conjugated *via* a labile linker to MMAE, an auristatin derivative and a potent microtubule inhibitor, with potential antineoplastic activity. The monoclonal antibody moiety of MLN0264 selectively binds to GCC and upon internalization and proteolytic cleavage, MMAE binds to tubulin and inhibits its polymerization, resulting in G2/M phase arrest and tumor cell apoptosis in GCC-expressing tumor cells. Currently a Phase -1 clinical trial is ongoing to assess the efficacy, safety and tolerability of MLN0264 in patients with recurrent or metastatic guanylyl cyclase C

(GCC)-positive adenocarcinoma of the stomach or gastro-oesophageal junction. It is also predicted to be a suitable treatment option for pancreatic cancer as a monotherapy agent or in combinational chemotherapy (Cruz Zambrano et al. 2014; Zhang et al. 2013; Teng et al. 2014).

3.2.6 Nemertea

DMXBA/GTS-21 (Alzheimer): DMXBA (GTS-21) (Fig. 3.2) is a synthetic analogue of anabaseine, which is currently in phase II studies. GTS-21 promotes the cognitive functions in experimental animals and humans. Anabaseine is present in various species of carnivorous marine worms, belonging to the Phylum Nemertea. GTS-21 selectively stimulates various types of animal nicotinic acetylcholine receptors such as α12β1γδ (embryogenic) or α12β1γε (adult) and α7 AChRs (Kem et al. 2006).

3.2.7 Rhodophyta

Digenea Simplex
Kainic acid (Anthelmintic): Kainic acid (Fig. 3.2) was originally isolated in 1953 from the red seaweed *Digenea simplex*, commonly known as "Kainin-Sou" (Davies 2007). It is used for nematodal infections in Japan. Additionally, it acts as a potent neuroexcitatory amino acid agonist to kainite receptors. Based on a dose response, it acts as a CNS stimulant in low doses, whereas as a neurotoxin at 10–30 mg/kg in mice. Kainic acid is used in laboratory animal models to study epilepsy and Alzheimer's disease (Baker 2015).

Rhodophyta
Iota-carrageenan (Antiviral): Iota-carrageenan (Fig. 3.2) is a linear sulphated polymer isolated mainly from red edible seaweeds belonging to the Rhodophyta. Also available as an Over-The-Counter (OTC) drug, it is a broad spectrum anti-viral molecule, which prevents the virus attaching to the cell by acting as physical barrier. It is proven to be effective for the prevention and treatment of (a) the common cold and influenza and (b) adenoviruses causing conjunctivitis (Eccles et al. 2010; Grassauer et al. 2008; Girond et al. 1991).

3.2.8 Fungi

Acremonium Chrysogenum **(Ascomycota)**
Cephalosporin C (Anti-infective): Cephalosporin C, one of the well-known β-lactam antibiotics, was isolated initially from the marine derived fungus, *Acremonium chrysogenum*, previously known as *Cephalosporium* sp. Cefalotin is a synthetic analogue of cephalosporin C, which is the first marketed cephalosporin antibiotic,

used because of its high potency compared to cephalosporin C (Fig. 3.2) (Abraham and Newton 1961).

3.2.9 Bacteria

Salinispora Tropica **(Actinobacteria)**
Salinosporamide A: Salinosporamide A (Marizomib®; NPI-0052) (Fig. 3.4) is a structurally and pharmacologically unique β-lactone-γ-lactam discovered from the marine actinomycete, *Salinispora tropica* and is a potent proteasome inhibitor. It is currently under phase-1 trials sponsored by Triphase Corporation. Marizomib, is established as an efficient single agent and in combination with biologics, chemotherapeutics and targeted therapeutic agents in models for (a) multiple myeloma, (b) Waldenstrom's macroglobulinemia, (c) chronic and acute lymphocytic leukemia, (d) mantle cell lymphoma and (e) glioma, colorectal and pancreatic cancer models through extensive preclinical evaluation in a variety of hematologic and solid tumor models. Marizomib has also exhibited synergistic activities in tumor models in combination with bortezomib, various histone deacetylase inhibitors and the immunomodulatory agent lenalidomide (Revlimid®) (Nett et al. 2009; Fenical et al. 2009).

Treatment of multiple tumor cell lines with marizomib and the histone deacetylase inhibitor, vorinostat, resulted in a highly synergistic antitumor activity. The combination of full dose marizomib with vorinostat is reported to be tolerable in patients with safety findings and consistent with either drug alone. These studies were granted the framework for continued clinical trials in patients with multiple myeloma, leukemias, lymphomas, and solid tumors. The compound is also expected to be an alternative for those patients who have failed bortezomib treatment for multiple myeloma, and in those where other proteasome inhibitors have not demonstrated significant efficacy (Potts et al. 2011; Millward et al. 2012; Ling et al. 2010). See also:

- *Streptomyces antibioticus* (Actinobacteria) (and *Tethya crypta*) above
- For the work on Vidarabine (Antiviral): Vidarabine (Ara-A) see Sect. 3.1.1 Porifera

3.3 Screening Marine Chemical Libraries

The results obtained over the decades in the search from new drugs from the sea, show several successes that have had major benefits to society. However some of the methods employed in the discovery of these compounds could be considered questionable. At the beginning of the twenty-first century several countries realized the huge potential of their marine bioresources and the benefits that could accrue. They demanded that legislation was put in place to protect their genetic resources, e.g. the

Convention on Biological Diversity and in particular the Nagoya Protocol. Given the potential marine resources that remain untapped in many countries, applications of these recent legislations are required to ensure the rights of each country are properly safeguarded (Lallier et al. 2014). Very importantly, the ABS Capacity Development Initiative was established in 2006 to support the development and implementation of national regulations on "Access and Benefit Sharing" (ABS) and also involves the marine environment especially in the Pacific and Caribbean Islands (http://www.abs-initiative.info/about-us/). Due to the broad remit of marine bioprospecting, legislation on bioprospecting in waters that are outside of any particular countries territorial waters might also be necessary.

In order to ensure maximum societal benefits from bioprospecting, each maritime country should be able to organize expeditions with the combined goals of documenting and describing their biodiversity and collecting samples for biodiscovery. The convention on biological diversity and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (Nagoya Protocol) have established a strong basis for a more sustainable and equitable use of marine bioresources (Lallier et al. 2014). Marine biodiscovery and prospecting should be performed with the assistance of the international scientific community if the expertise does not exist in that country. Well organized biorepositories should be set up in all countries or in international facilities and legislations on the use of this resource established (Fig. 3.5). In this sense the examples of Australia (WA Marine Bioresources Library), Norway (Marbank – National Marine BioBank) and Ireland (Repository of the Marine Institute) should inspire other countries and especially those with access to a rich marine biodiversity. The richness of our oceans is a resource that should be protected and used for the benefit of all humanity.

One of the principal shortfalls of the previous approaches was the lack of correct taxonomic identification of the taxa discovered. In most cases only the species leading to bioactive compounds were identified. It is time to support the proper taxonomic identification of marine species including the use of DNA sequencing. In addition to taxonomic identification, much more work is required in describing common macro-invertebrates as conservative estimates are that only one-third to one-quarter of marine species have been formally described (Appeltans et al. 2012). Both approaches are needed to better understand and sustainably exploit, our marine biodiversity.

The second step of the process should include the study of the metabolome of all collected species. Whilst this is a long term aim, it is necessary to help describe the chemical richness of our oceans as much as its biological diversity. The role of natural product chemists is therefore essential towards this end and the benefits are numerous: (i) the construction of a chemical library will accelerate the process of finding hits through a more efficient dereplication processes; (ii) the ecological role of these compounds could be assessed; (iii) biochemicals as used in chemotaxonomy, will contribute essentially to an integrative approach to systematics hence assisting the search for novel sources of active compounds; (iv) more solid hypotheses would be proposed for metabolic pathways hence facilitating biological synthesis; and (v) a

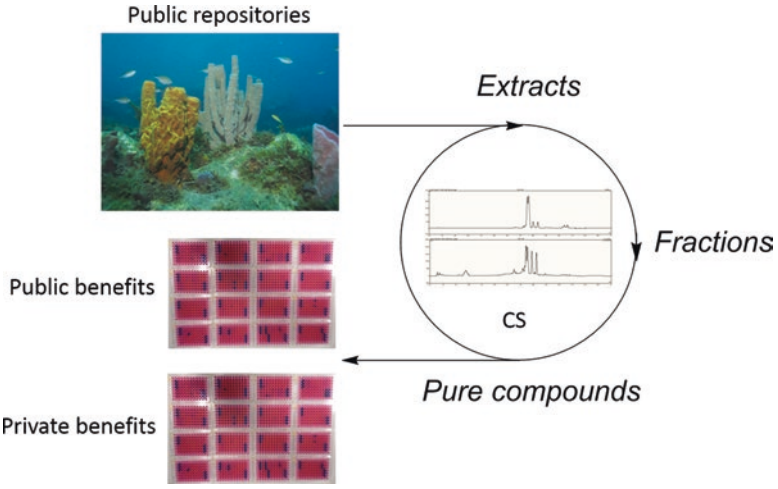

Fig. 3.5 Marine biodiscovery in the context of the construction of chemical libraries

large array of biological activities may be screened. Finally, we have to shift from a bioguided approach whereby a large number of extracts derived from marine organisms are investigated randomly in order to identify a small number of bioactive compound to a more constructive and environmentally sustainable approach whereby one compound is screened against a large array of bioassays in order to find its best target.

These goals will be obtained through strong collaboration and interdisciplinary research, where natural product chemists are key partners in this process. Since large pharmaceutical companies usually hold the intellectual rights to the research, the chemists will have to choose between interacting solely with companies and pharmacologists in the search for potentially large financial benefits, or to work in strong collaborations with marine biologists, microbiologists and ecologists for fewer monetary rewards. Although the latter approach may be more time consuming, it will enable a better understanding of our oceans and the resources they contain, which in the long-term will be of much greater benefit for the sustainable use of the ocean's resources and ultimately the future of humanity.

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