Blue Biotechnology

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BIOTECHNOLOGY IS DEFINED as the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services (OECD). Marine or Blue Biotechnology encompasses the application of biotechnology tools on marine resources.

Marine organisms used for Blue Biotechnology can be both microorganisms, such as bacteria, fungi, and microalgae, or macroorganisms, such as macroalgae and mussels. They are directly used as biomass or as producers of valuable ingredients such as active biological compounds, pigments, antioxidants, vitamins, fatty acids, enzymes, polymers or other biomaterials.

High value marine products and technologies can have a wide range of applications in health, food, feed, cosmetics, aquaculture, agriculture, industrial processes, environmental remediation, environmental monitoring and research tools.

A variety of techniques are used in the field. Among them are the fermentation using bioreactors, microbiological and chemical techniques, as well as cell-, gene-, protein- and other molecule-based techniques.

Blue Biotechnology: The Future Is Now

Introduction

Over the last decades, interest in Marine Biotechnology has steadily increased as it has considerable potential to address global challenges related to population health and environmental sustainability and to serve as an engine for greener and smarter economies.

The application of biotechnology to marine resources has already yielded some notable and wide ranging advances in the fields of medicine, cosmetics, nutraceuticals (food products with benefits for human health), food production and environment and industrial applications, with related consumer needs only expected to rise in view of demographic change, increased disease incidence and growing environmental concerns.

By comparison with terrestrial resources, marine resources are largely untapped. It is thus expected that they can provide a new important resource for the identification of valuable ingredients. Indeed, with a yearly growth rate of 12 % patents associated to genes of marine organisms amounted to 4,900 by 2010,[1] indicating the high potential for an economic valorisation of marine products. The use of marine bioresources for biotechnological applications is no longer a futuristic vision but a growing source of business opportunities.

At the moment, the global Blue Biotechnology industry is still nascent and very much focused on research and development. It still has a limited economic performance and plays only a small part within the overall biotech market. But numerous studies[2] project major growth, huge demand and correspondingly large markets for marine biotechnology. The Marine Board of the European Science Foundation predicts a leadership role for research in Marine Biotechnology in Europe by 2012, with a market estimated at € 2.8 billion.[3]

Though technical competences are available in several of the Baltic Sea Region countries, Blue Biotechnology still plays a relatively small role in the economies and development plans of the region. However, the basic elements are there for the sector to be able to expand rapidly as long as the challenges existing in the transfer from research to commercial application will be coped, including financial support (see section on "Knowledge Gaps"). Also, the relevant actors in the region can stimulate the political will to promote and implement a joint and coherent development strategy.

Baltic Sea Organisms

A common feature of Baltic Sea organisms is the fact that their diversity is rather unexplored with respect to potential for biotechnological applications. Much of research has so far focused on organisms from other sea areas (esp. Pacific Ocean). Nevertheless also the Baltic Sea harbours a great diversity of marine organisms, which provide a great potential for exploitation.

As a brackish water body, one that is more saline than freshwater but less than seawater, the Baltic Sea comprises a diverse combination of freshwater and marine groups of microorganisms, with indigenous populations that have adapted to these unique conditions.[4] According to census estimates, the Baltic Sea hosts at least 6,065 species, including at least 1,700 phytoplankton, 442 phytobenthos, 1,199 zooplankton, 569 meiozoobenthos, 1,476 macroozoobenthos, 380 invertebrate parasites, about 200 fish, 3 seal and 83 bird species.[5]

It stands to reason that given the considerable species diversity of these waters, the potential for finding compounds of interest for application development is also significant. For example, it has been shown that some bacteria associated with macroorganisms from the Baltic Sea such as the alga *Saccharina latissima,* the sponge *Halichondria panicea* and several bryozoan species exhibit a great potential for the production of antimicrobial compounds.[6, 7, 8] A few other examples are known of Baltic Sea microbial strains that produce bioactive compounds, as shown in table 1.

As a matter of fact working with Baltic Sea organisms implies also other advantages. Expedition costs

Table 1: Baltic Sea microbial strains known to produce bioactive compounds.

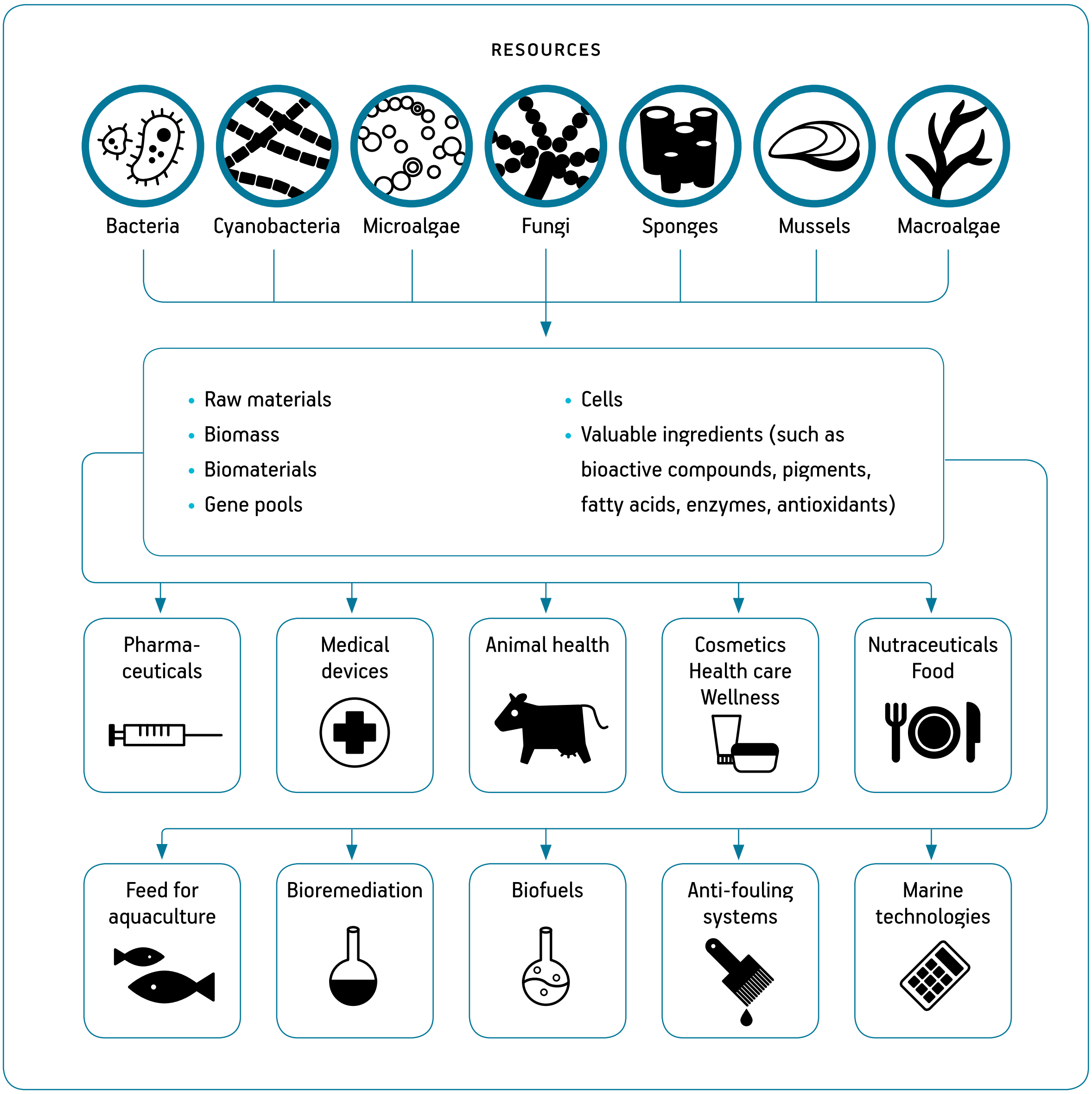
Compound	Produced by
Trophodithietic acid with antibacterial acitivity	*Roseobacter sp.*, a marine epiphytic bacterium[9]
Streptophenazines A-H with antibacterial activities	A strain of the bacterium *Streptomyces sp.* isolated from the sponge *Halichondria panicea*[10]
Mayamycin, a polyketide with inhibitory activity against a panel of tumor cell lines and antibiotic resistant human pathogens (patented)	A strain of the bacterium *Streptomyces sp.* isolated from the sponge *Halichondria panicea*[11, 12]
Tambjamine, a compound with the ability to kill nematodes	The bacterium *Pseudoalteromonas tunicata*[13]
Balticols A-F naphthalenone derivatives with antiviral activity against *Herpes simplex* virus type I	Fungal strain[14]
Compound Sch210972, an inhibitor of human leukocyte elastase playing a role in a severe lung disease	*Microplodia sp.*, a fungus obtained from the green alga *Enteromorpha sp.*[15]

to other sea areas are very high. Furthermore cultivation of indigenous organisms is much easier and legal as well as Intellectual Property questions are easier to be solved.

Applications

Blue Biotechnology has considerable potential to help address global challenges in population health, food security and industrial and environmental sustainability as well as protecting and preserving marine resources for future generations. The

Figure 1: Examples of the applications from various Baltic Sea microorganisms (e.g. bacteria, fungi, microalgae) and macroorganisms (e.g. sponges, mussels, macrooalgae) as sources of high-value products providing benefits for science and industry, for human health and environment as well as for growth and economy development of the Baltic Sea Region.



exploitation of marine micro – and macroorganisms is a promising tool to find solutions to these challenges through provision of products for the pharmaceutical industry, the medical field, human diet, animal feed, the cosmetics and wellness sectors, bioremediation and other purposes (Figure 1).

Pharmaceutical Industry

As the global incidence of infectious diseases, cancer, heart diseases, asthma, Alzheimer`s disease and diabetes continue to increase and simultaneously the number of antibiotic-resistant pathogens also grows, the need for development of new drugs has become ever more important, also with respect to an increase of the elderly population. Generally, natural products play an important role in the development of drugs, with 63 % of new drugs classified as naturally derived. Marine compounds show remarkably high hit rates in the screening for drugs.[16] More than 20,000 marine active compounds have been found until now with 80 % showing anticancer activity. Approved drugs are Cytosar-U®, Vira-A®, Prialt®, Halaven®, Lovaza®, Yondelis® and Adcetris®. A further successful example is the substance pseudopterosin, isolated from corals grown in mariculture in the Bahamas[17] which shows potential activity against psoriasis and neurodermatitis, inflammatory diseases, pain and rheumatic disease. The substance is in clinical trials phase II.

There is growing interest particularly in the exploitation of marine bacteria and fungi because microbial secondary metabolites, those organic compounds produced by the organism and involved in factors such as fecundity, survivability or defence, provide promising new structures for drug discovery[18,19] and because a sustainable production of these bioactive compounds can be ensured by fermentation processes. Advances have been made in the identification of antimicrobial and antitumor compounds as sources for new anti-infective drugs and drugs for the treatment of cancer respectively.[20,21,22] Examples of bioactive compounds which were produced by microorganisms from Baltic are given in the section on “Baltic Sea Organisms”. Table 2 gives an overview of the global marine pharmaceutical pipeline.

Table 2: The global clinical pipeline of marine pharmaceuticals as of July 2012.[23,24]

Compound Name	Trademark	Marine Organism	Company or Institution	Disease Area
Clinical Status: Approved				
Cytarabine, Ara-C	Cytosar-U®	Sponge	Bedford	Cancer
Vidarabine, Ara-A	Vira-A®	Sponge	No information available	Antiviral
Ziconotide	Prialt®	Cone snail	Azurpharma	Pain
Eribulin Mesylate (E7389)	Halaven®	Sponge	Eisai Inc.	Cancer
Omega-3-acid ethyl esters	Lovaza®	Fish	GlaxoSmithKline	Hypertriglyceridemia
Trabectedin (ET-743)	Yondelis®	Tunicate	PharmaMar	Cancer
Brentuximab vedotin (SGN-35)	Adcetris®	Mollusk	Seattle Genetics	Cancer

Compound Name	Trademark	Marine Organism	Company or Institution	Disease Area
Clinical Status: Phase III				
Plitidepsin	Aplidin®	Tunicate	PharmaMar	Cancer
Clinical Status: Phase II				
DMXBA (GTS-21)	–	Worm	University of Colorado Health Sciences Centre	Cognition Schizophrenia
Plinabulin (NPI 2358)	–	Fungus	Nereus Pharmaceuticals	Cancer
PM00104	Zalypsis®	Mollusk	PharmaMar	Cancer
Elisidepsin	Irvalec®	Mollusc	PharmaMar	Cancer
PM01183	–	Tunicate	PharmaMar	Cancer
CDX-011	–	Mollusk	Celldex Therapeutics	Cancer
Tasidotin, Synthadotin (ILX-651)*	–	Bacterium	Genzyme corporation	Cancer
Clinical Status: Phase I				
Marizomib (Salinosporamide A, NPI-0052)	–	Bacterium	Nereus Pharmaceuticals	Cancer
PM060184	–	Sponge	PharmaMar	Cancer
SGN-75	–	Mollusk	Seattle Genetics	Cancer
ASG-5ME	–	Mollusk	Seattle Genetics	Cancer

* – Phase II has been completed

Cosmetics, Health Care and Wellness Products

In cosmetics, surfactants („surface active agents") are compounds that lower the surface tension of a liquid or that between a liquid and a solid and are thus used as cleansers, detergents, solubilisers, foaming agents and emulsifiers. Surfactants can be found in almost all kinds of products based on powders, liquids, lotions, creams, gels and sprays.

In tune with current ecological concerns, chemical surfactants are giving way to biologically produced surfactants such as phospholipids, lipopeptides and glycolipids originating from marine organisms (Table 3). In contrast to conventional surfactants, bio-surfactants are completely biodegradable and hence environment-friendly. Furthermore, they are less toxic and more stable over a wide range of temperatures and pH. Alone in 2006, 255 patents related to bio-emulsifiers and bio-surfactants were issued (33 % in the petroleum industry, 15 % in the cosmetics industry, 12 % in medicine and 11 % in bioremediation).[1] The exploitation of these patents could enhance the output of marine products containing surface active compounds.

Several companies in Europe already successfully market cosmetics containing compounds of marine origin. Examples are Esteé Lauder with Resilience®, a product containing the pseudopterosin compound is used as an additive preventing irritation caused by exposure to the sun or chemicals,[25] Aqua Bio Technology ASA (Norway), with Aquabeautine XL®, a skin care product con-

Table 3: Examples of surfactant-producing bacteria and fungi used for cosmetic applications.

Microorganisms	Surfactant	Effect	Product
Candida bombicola	Sophorolipids	Moisturizing, foaming, emulsifying	Deodorants, body washes, and acne treatments
Pseudomonas aeruginosa	Rhamnolipids	Anti-microbial, emulsifying	Anti-wrinkle and anti-aging cosmetics
Candida antarctica	Mannosylerythritol lipids	Emulsifying, dispersing	Smoothing and anti-wrinkle products

taining proteases and proteins from salmon and Daniel Jouvance (France) and Thalgo Cosmetic (France, Germany), with micro – and macroalgae based cosmetics.

Enzymes for Industrial Processes

In the frame of the Europe 2020 Strategy the European Commission calls for "Innovating for Sustainable Growth: A Bioeconomy for Europe" which addresses the sustainable use of renewable resources for industrial purposes in 2012.[26] It is also already a trend and one which is expected continue growing, to replace more and more chemical products and processes with biologically-based ones, as they are more environmentally friendly and thus have higher acceptance among consumers. For example, cold-adapted enzymes, those synthesised by organisms that thrive in cold environments, are now being used to improve industrial processes as they allow for the reduction of the water temperature and thus the energy required for a process. Currently, 40 % of the total sale of enzymes applies to proteases, lipases, amylases and cellulases used as additives in detergents in order to reduce the temperature required for washing.[27]

Another useful benefit of cold-adapted enzymes is that they can be inactivated with mild heat. This is

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Raw materials or extracts from Baltic Sea macroalgae species have already been used for cosmetic and health care products. Species such as *Agarum cribosum* or those of the *Laminaria* genus have been used to manufacture anti-aging formulas due to their hydrating properties. The red microalgae *Porphyridium sp.* and *P. aerugineum* have natural active shield released to the proximate surroundings, creating a thick protective layer around the cell. This was incorporated in the hydrogel *Alguard*™, manufactured by Frutarom to provide quick beauty skin protection.

In Estonia, curative mud originating in Haapsalu Bay, Käina Bay and the Mullutu coastal lake are increasingly being used for wellness, thalasso therapy and care in medical spas (see also "Reed Harvesting" chapter). A number of cosmetic and health care product manufacturing companies in the Baltic Sea Region already market products based on components produced by marine organisms or containing marine ingredients.

Table 4: Examples of cosmetic and health care manufacturing companies in the Baltic Sea working with marine organisms.

Company	Product
ORTO (Estonia)	Cosmetic products from sea mud from Haapsalu
GoodKaarma (Estonia)	Organic soaps made from sea mud from Haapsalu
MADARA (Latvia)	Macroalgae based cosmetics
oceanBASIS (Germany)	Oceanwell and o'well med cosmetic series made from brown macroalga *Saccharina latissima*, Ocean Collagen Pro Age containing collagen from a marine organism
AQUAZOSTA MB (Germany)	MAREZOSTIN® cosmetic/thallasso-wellness products derived from eelgrass *Zostera marina*
Heitland & Petre International GmbH (Germany)	Maresome® derived from cyanobacteria *Anabaena sp.* with activity against skin bacterial infections caused by multiresistant *Staphylococcus aureus* (MRSA)
Ocean Pharma GmbH (Germany)	CuraMar® algae based products for nail care
Inwater Biotec GmbH (Germany)	Algae based cosmetics
La Mer (Germany)	Skin care products using mud from the Wadden Sea
Meereskosmetik Macon (Germany)	Cosmetics from marine extracts
Dalton Kosmetik (Germany)	Skin care products based on sturgeon extracts
Biomaris (Germany)	Skin care products with active ingredients from sea minerals and seaweed

particularly useful in those industrial processes in which the contact of the enzyme with the substrates to be transformed should be limited in time so as to prevent excessive or deleterious action. An example is that of cellulases used in the textile industry for stonewashing, i.e. the process of producing a worn appearance on textiles, in which the excessive action of the enzymes could lead to the loss of mechanical resistance of the cotton fibres.

Cold-adapted enzymes are also used in the food processing industry, with meat tenderising with proteases as the best example. As an example, the food manufacture Unilever has developed a low fat ice cream containing an anti-freeze protein from the Arctic ocean pout, cold-water fish.[28] Other applications include the removal of lactose in milk with β-galactosidases and the improvement of the volume and crumb quality in bread with xylanases.[29] Some additional examples of enzymes, which can be useful for industrial processes, are listed in Table 5. In the near future, it is expected that other applications such as enhancing extraction yield, enhancing fruit juice taste by pectinases and developing new tastes and flavours with lipases will also be implemented. Research and /or application of enzymes from marine organisms is not only performed e.g. by ArcticZymes (Norway) but also by companies located at the BSR, such as Enzymicals AG (Germany), BRAIN (Germany) or DANISCO (Denmark).

Table 5: Examples of enzyme use for industrial processes.

Enzyme	Synthesizing Microbe	Property	Industrial Use	References
Protease	Symbiont in ship-worm	Alkaline pH	Cleansing additive	Greene, 1996[30]
	Bacillus mojavensis	2 detergent stable serine proteases	Detergent	Haddar, 2009[31]
Lipase	*Penicillicum oxalicum, Aspergillus flavus*	Cold-adapted	Detergent, paper production	David, 1935[32]
Phospholipase C	Marine streptomycete	Optimum at pH 8 and 45°C; only hydrolysis of phos-phatidylcholin		
Alginate lyase	Algae, marine invertebrates, microbes		Novel alginate polymers	Wong, 2000;[33] Xiao, 2006;[34] Alkawash, 2006;[35] Gacesa, 1988,[36] Gacesa, 1992[37]
Agarases	Agarolytic microbes	Softening or lique-fying of agar	Processes for pro-duction of bever-ages, bread and low-calorie foods	Rasmussen, 2007;[38] John, 1981;[39] Oren, 2004;[40] Yaphe, 1972;[41]; Aoki, 1990;[42] Leon, 1992;[43] Hosoda, 2003;[44] Sugano, 1993[45]
Carrageenase	Red seaweeds, marine molluscs, marine bacteria		Coagulant, adhe-sive, stabiliser, emulsifier	Sarwar, 1987;[46] Roberts, 2007[47]
Amylase	Bacteria, fungi, sponges		Bread-making process	Gupta, 2003[48]
Cellulose and hemicellulose hydrolase	Bacteria, fungi		Bio-textile auxil-iaries, cotton and linen process-ing, bio-fertiliser processing, sea-weed degradation	Klemm, 2005;[49] Tong, 1980;[50] Doi, 2008[51]
Fibrinolytic enzymes	Bacteria	High stability towards various surfactants and oxidizing agents	Laundry detergent, thrombolytic agent	Mahajan, 2012[52]

Food and Feed Products

Numerous food supplements can be traced back to compounds of marine origin. Microalgae, for example, are commonly used as a food supplement, with some of the most valuable products being polyunsaturated fatty acids (omega-3 fatty acids) and antioxidants (e.g. β-carotenoid).[53]

From the aquaculture perspective, there is a great challenge in providing new cheaper feed products, as the feed constitutes about 50 % of the cost drivers (for fish). New healthy feed products are also necessary to prevent diseases and to enhance the quality of the cultivated organisms. Animal proteins should be replaced by plant products, such as those from algal origin. Cultured microalgae are already used as a feed additive in mollusc and shrimp aquaculture[54] as well as in feed for poultry, pigs and some pets.[55] The microalgae pigment astaxanthin is an especially valuable feed additive in salmon farming, giving the pink colour of the fish meat.

Biomaterials

Though this is still a very new field, over the past decade the medical, pharmaceutical and biotechnological industries have directed increasing attention towards biomaterials such as biopolymers of marine origin. Microbial biopolymers are polysaccharides, chitins or collagens, which have numerous applications ranging from bioplastics (such as polyhydroxyalkanoate, also know as PHA, which is synthesised by various marine bacteria) to pharmaceutical and

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Research on microalgae high value compounds from the Baltic Sea Region for use as food and feed supplements has been quite limited, though several Lithuanian studies have looked into the use of *Spirulina* and *Chlorella* microalgae as dietary supplements for humans and animals.[56, 57, 58, 59]

Production is thus far mostly small scale but several companies throughout the region have successfully marketed various (mostly algae-based) compounds for use in the food and feed industries.

Table 6: Examples of Baltic Sea Region companies and institutions investigating or producing food and feed additives from marine organisms

Products	Company/Institution
Spila Spirulina as food additive and Spilamix as feed additive, from *Spirulina platensis*	SPILA UAB (Lithuania)
Nutraceuticals and feed additives	BlueBio Tech GmbH (Germany)
Nutraceuticals	Biovico (Poland)
AstaREAL® astaxanthin from microalgae Haematococcus pluvialis	Bioreal AB (Sweden)
Algae food, chitofood (using chitin from crustacean shells)	ttz Bremerhaven (Germany)
Omega-3 fatty acids	Finnish Environment Institute – SYKE (Finland)

Unsaturated fatty acids, especially docosahexaenoic acid (DHA) as a food supplement	MareNutrica (Germany)
Food supplements such as omega-3 from microalgae	SimrisAlg (Sweden)
Alternatives for fish feed and fish meal using in vitro fish cell cultures	Fraunhofer Research Institution for Marine Biotechnology EMB (Germany)
Colourants for food and feed	Sea & Sun Technologies GmbH
Food supplements such as polyunsaturated fatty acids from microalgae and processing of innovative products	IGV GmbH (Germany)
Products with *Chlorella* as food supplement (tablets, powder, bread, pasta, sweets)	Roquette Klötze GmbH & Co KG (Germany)

medical polymers for sealing wounds, bio-adhesives, dental biomaterials, tissue regeneration and 3D tissue culture scaffolds.[60] As an example products of the company HemCon Medical Technologies (USA), such as HemCom® Bandages PRO, are based on chitosan.

In comparison to conventional polymers, biopolymers have the advantage of being biodegradable, less toxic and based on renewable resources. Marine biopolymers may have a major future market potential but are currently still in development stage.

Bioremediation of Marine Ecosystems

This relatively novel application involves the use of oil-degrading bacteria to improve water quality. Oil is a complex mixture of hundreds of different compounds generated from dead biomass over millions of years. In parallel, certain microorganisms, some of which are a common part of the marine microbial community in the Baltic Sea, have developed special enzyme systems to be able to use some of the oil components as substrate. Research is therefore going into the identification of microorganisms that might be able to mitigate the negative effects of accidental oil contamination from ship accidents or leakage of oil platforms.

So far, no microbes are known that are able to degrade the whole spectrum of oil components. To estimate the amount of active oil-degrading species as well as the cocktails of enzymes they produce for these purposes will require both molecular-ecological and metagenomic approaches. But the starting point is an encouraging one, as investigation of the microbial diversity in Baltic Sea sediments has already revealed the presence of microbial strains possibly involved in degradation of the pollutant phenantrene.[61]

Anti-fouling Systems

Surfaces in the marine environment are rapidly colonised by microorganisms such as bacteria, a process which is then followed by colonisation by macroorganisms such as barnacles. This usually poses a problem for ships when a biofilm grows on the bottom, resulting in reduced cruising speed, high fuel consumption and thus increased CO_2 emissions.[62] Anti-fouling coatings are thus used containing chemical substances that prevent the formation of biofilms. Because these coatings often have toxic effects, legal regulations such as the International Convention on the Control of Harmful Anti-Fouling Systems on Ships (AFS Convention) – adopted in 2001 by the International Maritime Organisation – are in place to promote restriction or even ban of toxic compounds such as tributyltin (TBT) used for anti-fouling.

Marine bio-based coating with anti-fouling and anti-corrosive properties may offer new solutions to the shipping industry. This promising new research field is investigating marine bacteria for their potential to produce compounds exhibiting anti-fouling activities. Since marine organisms have developed defence strategies against competitors and antagonists, they are involved in processes preventing fouling as it was shown for bacterial biofilms being active against barnacle attachment in the Baltic Sea.[63] Recent studies in Danish coastal waters have found marine bacteria showing anti-adhesive effects on a biofilm-producing *Pseudoalteromonas* sp. bacterium as well as on zoospores of the green alga *Ulva australis*.[64] Further research is still needed to identify the bioactive compound(s), conduct an Environmental Risk Assessment and develop a process for manufacturing an anti-fouling system based on this compound. The development of anti-fouling systems is carried out e.g. by the University of Gothenborg (Sweden) and the company LimnoMar.

Biofuels

The aspect of using biomass from marine organisms for the production of biofuels is covered in chapter 3 "Macrogalgae Harvesting and Cultivation" and chapter 6 "Microalgae Cultivation".

Technology

Technological pre-conditions: from finding towards scale-up

Two phases can be distinguished in the search for valuable ingredients from marine micro – and macroorganisms, which require different kinds of technical equipment:

In the 1st Phase focus lies on "finding" organisms with interesting characteristics for a wide spectrum of possible applications (figure 2 shows the steps involved in drug discovery): In this phase it is essential to build and conserve microbial culture collections that keep the strains available for further investigation and production. In order to get the desired compounds from the cultivation experiments, extraction methods are performed using, for example, organic solvents. For the purification of compounds and the elucidation of their structures several techniques are employed, among them high-performance liquid chromatography (HPLC), mass spectrometry (MS), nuclear magnetic resonance (NMR), gas chromatography (GC) and fast centrifugal partition chromatography (FCPC®). Known compounds produced by the organisms in cultivation experiments must be quickly identified to avoid 'rediscovering' of already known compounds. The marine natural products in substance libraries have to be maintained in high purity and high amounts in order to provide enough material for high throughput screening procedures with the aim to apply as much as possible test systems. For example, the search for new drug candidates requires a broad range of screening panels using bioassays relevant for human health; i.e. assays for determining the inhibitory activity of compounds against antibiotic resistant human pathogens, against tumour cell lines or enzymes playing a key role in diabetes or Alzheimer´s.

After establishment of the process at laboratory scale the 2nd Phase starts, in which it is necessary to prove reproducibility and to scale-up the production to ensure the amounts of biomass and substances required at all stages of product development to enable commercial production according to the industrial requirements. Scale-up involves the use of fermenters (10–3,000 L or even higher) for the cultivation of the bacteria, fungi or microalgae strains that will be producing the compounds (figure 3). In case of the cultivation of macroorganisms the availability of appropriate systems for mariculture or aquaculture is essential for a high yield in biomass. Subsequently the so called downstream processing is carried out comprising technologies which are necessary to separate and to purify the desired ingredient from the biomass e.g. by mechanical, analytical and preparative separation

Figure 2: "Finding Phase": Summary of steps involved in the exploration of marine natural products from microorganisms for drug discovery.[65] The path of isolation of microbes from the marine habitat in order to gain bioactive compounds for further drug development is illustrated. Once bacteria and fungi have been brought into pure culture, straightforward procedures are available to cultivate them in larger volumes, to chemically analyse the natural products and identify the compounds, as well as to optimise the production by strain selection and elaboration of the optimal physicochemical conditions for production. This includes design and development of the fermentation process and selection of strains from a larger panel of similar strains that produce the desired compound as well as strain improvement by random or directed genetic manipulation.

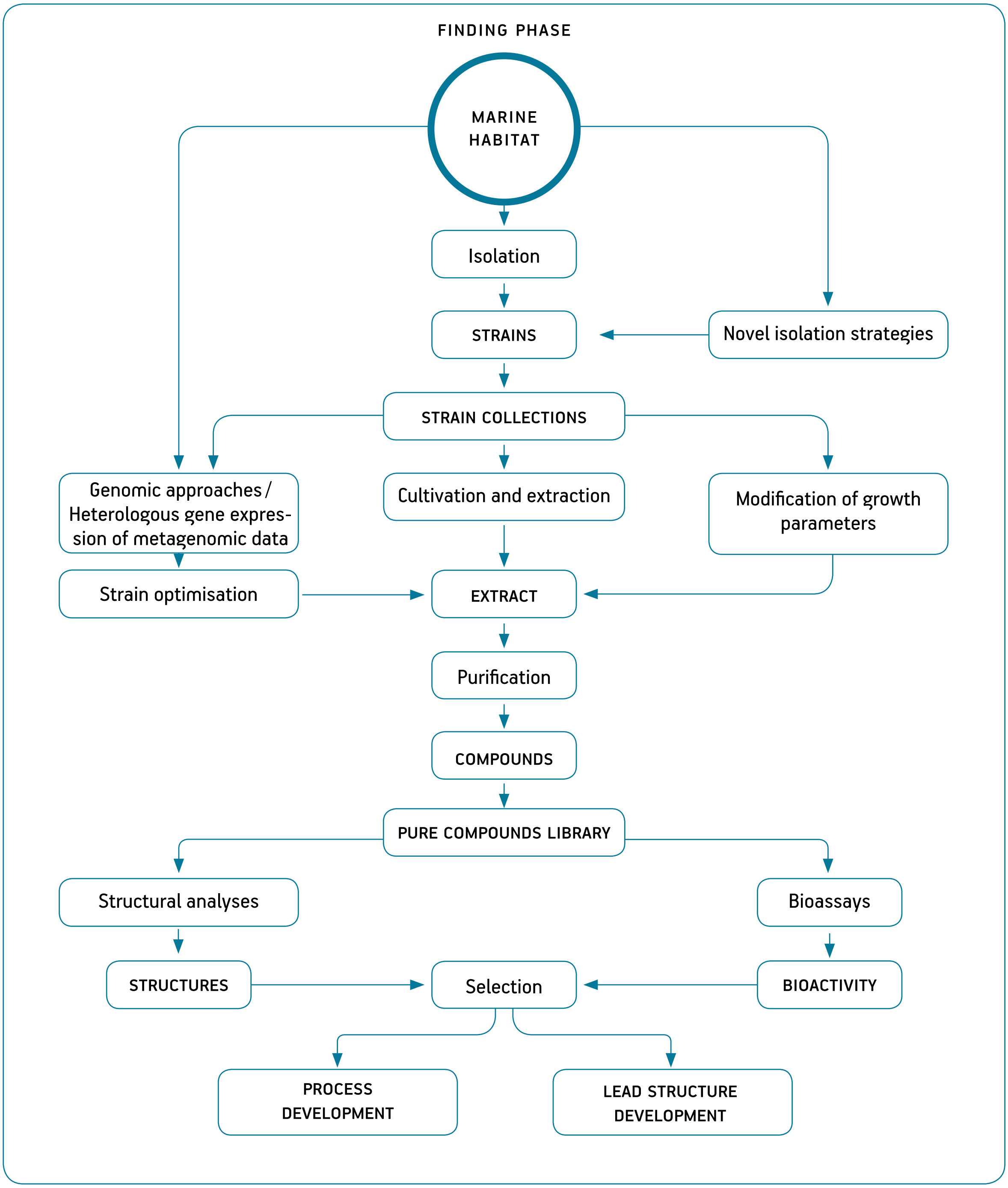


Figure 3: Fermenter at GEOMAR | Helmholtz Centre for Ocean Research Kiel.

technologies, such as centrifugation, the use of absorbers, and/or chromatography. Dependent on the intended purpose of the purified ingredient several steps follow to develop the market product, e.g. to evaluate the sufficient concentration to be used, the suitable formulation or the proper carrier-material for specific technological applications.

GENOMIC TECHNIQUES

Despite the success of the traditional culture-based, bioassay-guided strategies used to discover new natural products, genetic analyses have revealed that these approaches provide access to only a small fraction of the biosynthetic capacity encoded in microbial genomes. This is because more than 99% of all bacteria are to date still not cultivable under laboratory conditions. Also, the majority of biosynthetic pathways are only expressed scarcely or not at all under laboratory conditions and the products of these pathways have been overlooked.[66] This means that a microorganism may have the potential to produce a promising drug candidate but the conditions for inducing the production of this compound are unknown. Therefore, several genetic techniques are performed with the aim of accessing these compounds.

One approach is the analysis of the full genome sequence of a cultivated strain or a single cell obtained directly from the environment. This allows the detection of genes coding for metabolites that have the potential to exhibit promising properties. Several genomics-inspired strategies have been applied in unveiling new metabolites.[67] Among these strategies is the scanning of genomes to predict chemical structures from genes and the transfer of genetic material coding for compounds of interest from marine microorganisms into easily grown "producer strains" such as *Streptomyces* sp. bacterial strains.[68, 69]

There is strong evidence that the marine pharmaceutical pipeline as well as the portfolio of new enzymes will be up-scaled in the near future with products from uncultivable marine bacteria. New metagenomic techniques, those focused on studying the genetic material recovered directly from environmental samples, will be increasingly applied with the aim of accessing this large gene pool containing information for valuable products. As an example Hardemann & Sjoling (2007)[70] detected a novel lipase from Baltic Sea sediment sample by a metagenomic approach. This enzyme might be used for industrial application because of its activity at low temperature.

Further technologies, such as the aquatic cell technology, which is based e.g. on fish or algae cells, respectively, for the production of valuable ingredients for feed and other applications or the development of biosensors by using e.g. genetic information or toxins from marine organisms also contribute to the sustainable use of marine biotechnology.

Laboratories in the Baltic Sea Region

In the Baltic Sea Region, the landscape of public institutions and private companies focusing on exploration and exploitation of marine organisms for biotechnology is relatively scattered and no systematic mapping has been conducted to assess the distribution of players and their roles, interests or technical expertise.

Overall the majority of activity appears to be focused in northern Germany as well as Denmark, but recently also individual institutions / researchers in Finland, Poland and Sweden have started to be active in EU financed projects such as MAREX, MARINE FUNGI and MicroB3.

Generally technical facilities in form of highly equipped laboratories exist in almost all countries throughout the Baltic Sea, because there is an increasing interest in biotechnology. A fact becoming evident e.g. by the initiatives of the Latvian Biotechnology Association (LBA), the feasibility study for an Estonian Biotechnical Programme[71] and from reports about biotechnology in Lithuania.[72] Many institutions have so far mainly worked on marine biodiversity research or in biotechnology at general level. But their equipment could be used with hardly any further investment for the exploitation of marine organisms as well. The Latvian JSC "Biotehniskais Centr" could for instance provide fermentation capacities for the cultivation also for marine microorganisms producing valuable ingredients for biotechnological products.

However, no network or strategy is in place to promote their awareness of each other at the level of the whole region – which would be a pre-condition to enable the sharing of their (expensive) capabilities and the knowledge generated in the field Blue Biotechnology.

Furthermore – whereas capacities seem to be sufficient for the 1st "Findings" Phase – there seems to be a lack in capacities for scale-up and downstream processing, i.e. process development. In this phase not only large scale facilities (e.g. 3000 l fermenters) are required, but also sophisticated organisational /quality assurance systems in order to comply to legal regulations (i.e. documentation) (see section on "Legal Aspects").

Competence Centres in the Baltic Sea Region

It goes without saying that Blue Biotechnology does not only require natural ingredients and sophisticated technology, but also highly specialised experts in such diverse disciplines like microbiology, zoology, genetics, chemistry and pharmacy. Whereas in early years, most research and development in the field of Marine Biotechnology was conducted in academic institutions from one disciplines, today's landscape of natural product development is much more diversified and tremendous amounts of investments are related to these activities.

Specialised Marine Biotechnology research centres have now been established all over the world, where all the necessary disciplines and expertise are bundled together to contribute to integrated research and developments. Several examples of these specialised research centres exist in Europe, including the Marine Biodiscovery Centre in England or the Department of Biotechnology at SINTEF Materials and Chemistry in Norway. Additionally, networks including research institutions and companies with a clear marine biotechnological core business have been established. One of these is the Marine Biotech Cluster in Tromsø, Norway.

In the Baltic Sea Region research centres with special expertise in different fields of Blue Biotechnology are located in almost all countries. Examples are given in table 7.

Table 7: Examples of research centres and EU 7th Framework Programme projects with a research focus on various fields in Marine Biotechnology.

Research Centres	Activities relevant to Marine Biotechnology
Northern Germany	
University Greifswald and associated Institute of Marine Biotechnology e.V IMaB	Natural products, marine enzymes, functional genomics, metabolomics, discovery of new drugs, biotransformation, nanoparticles and active compounds
Kieler Wirkstoff-Zentrum at GEOMAR (The Kiel Center for Marine Natural Products at GEOMAR)	Bioactive compounds from microbes, pure compound library, bioassays, genomics, process development, scale-up, discovery of new drugs and enzymes, research on the biological function of bioactive compounds and their producers at marine habitats; network "Blue Biotechnology"; Lead Partner to FP7 MARINE FUNGI
University of Bremen	Marine genomics, lead partner to FP7 MicroB3
Fraunhofer Research Institution for Marine Biotechnology EMB	Development of new technologies, processes and instruments in the fields of biological water quality control, aquaculture technology, stem cell isolation and utilisation (e.g. fish cells) and others
Institute for Marine Resources GmbH (IMARE)	Biosensors, mariculture, technical applications of marine structures / nanomaterials
Denmark	
Danish Technical University (DTU)	Marine bioactive compounds, Partner to FP7 PharmSea
University of Copenhagen KU-Science	Marine bioactive compounds, food and feed with marine-derived ingredients
Latvia	
Latvian Institute for Aquatic Ecology	Environmental monitoring
Finland	
Helsinki University	Lead Partner to FP7 Project "MAREX"
VTT Technical Research Centre of Finland	Partner to FP7 Project "MARINE FUNGI"
Lithuania	
Klaipeda University Coastal Research and Planning Institute (CORPI)	Marine bioactive compounds from microalgae
Estonia	
Estonian Marine Institute of University Tartu	Environmental monitoring
Competence Center of Food and Fermentation Technologies (Tallinn)	Food containing marine-derived ingredients
Sweden	
Finish Environment Insitute (SYKE)	Fatty acids from marine microalgae for diverse uses
University of Gothenborg (with MareLife, Norway)	INTERREG IVA project BlueBio (Blue Biotechnology for sustainable innovations in the region Öresund-Kattegat-Skagerrak)

Research Centres	Activities relevant to Marine Biotechnology
Poland	
University of Gdansk	Partner to FP7 MAREX, bioactive compounds from marine microalgae, marine genetics, environmental monitoring
Institute of Oceanology of the Polish Academy of Science	Marine bioactive compounds, marine genetics, environmental monitoring

Environmental Assessment

The full scope of environmental impacts that the Blue Biotechnology field may have on the marine environment is still difficult to assess. This is because much of the work is still in an experimental stage but also because generally exploration is supported by highly competitive commercial companies, so most of the research and development efforts are not published in the literature. Nevertheless, research on and application of marine biotechnology is not expected to have negative impacts on the environment. In contrast, marine biotechnology will include strong positive impacts.[73] Among them might be the reduction of environmental damages on marine environments and the improvement of the climate. Some preliminary issues can be elaborated on (Table 8).

Habitat and Species Protection

The disturbance of the biological environment that occurs with the extraction of the species and capture of non-target species is considered negligible. In one litre of water from the Baltic Sea or on the surface of a single leaf of algae there are millions of bacteria and thousands of fungi and microalgae each with the potential to produce valuable ingredients for human and environmental health. Therefore, only tiny amounts of the original sample (such as a piece of sponge, coral or sediment) are needed. Several laboratory enrichment and cultivation techniques are then used to make the microorganisms available for further research. In the case of macroorganisms (e.g. macroalgae, mussels) it is possible to cultivate them using aquaculture, whereby environmental damage by harvest from the habitat is avoided. In this case, environmental impacts associated with the cultivation of macroalgae or mussels should be considered (see "Macroalgae Harvesting and Cultivation" and "Mussel Cultivation" chapters).

The unknown consequences to habitats and species through the release of bioengineered compounds or bacteria into the marine environment are potentially of greater importance. The need for environmental monitoring and surveillance has been identified as a growing factor over coming decades.[73] Very little is known at this point about the impact of using bioengineered compounds or bacteria in the marine environment and further research and monitoring of these types of applications is required. It is essential that marine biosource compounds and bacteria be developed that can be safely used in the marine environment.

Water Quality

One important application of Blue Biotechnology is the development of marine bio-sourced compounds that can safely replace toxic anti-fouling or anti-corrosive agents currently used on ships and submarine installations, thereby improving water quality. In addition, there is the application of bioengineered bacteria for bioremediation purposes following pollution events. Furthermore, the development of monitoring and detection systems based on compounds such as microalgal or bacterial toxins produced by marine organisms and which are harmful to humans as allergens or contaminants in seafood could help prevent diseases caused by these toxins.[74, 75]

Table 8: Overview of Blue Biotechnology's impact on environmental objectives and priorities.

Environmental Objective	Environmental Priority	Impact of Blue Biotechnology
Water quality	Bathing quality	strongly supportive ?
	Water transparency	strongly supportive ?
	Eutrophication	strongly supportive ?
	Biogeochemical cycles	strongly not supportive ?
Habitat / Species protection	Food web dynamics	neutral ?
	Biodiversity	moderately supportive ?
	Benthic habitats	moderately supportive ?
	Bird habitats	moderately supportive ?
	Fisheries	moderately supportive ?
	Marine mammals	moderately supportive ?
	Marine noise	
Coastal protection	Coastal morphology	
	Scenery	
Climate protection	CO_2 Emissions reduction	strongly supportive

- strongly supportive
- moderately supportive
- strongly not supportive
- moderately not supportive
- neutral
- ? gaps in information
- blank not applicable

Large masses of plastic and plastic debris have been released into the environment, and thereby have entered the world´s ocean.[76] The use of alternatives, such as biodegradable products might contribute to resolve this long-standing problem, because degradation could be performed by enzymes produced by bacteria.[77]

Climate Protection

The main cause of the current global warming trend is the greenhouse effect. Microbial processes have a central role in the global fluxes of the key biogenic greenhouse gases (carbon dioxide, methane and nitrous oxide). With molecular-genetical approaches different groups of microorganisms should be identified which can dissimilate the organic part of the Baltic Sea water to carbon dioxide and therefore may enhance the greenhouse effect. If we understand the mechanisms of bacterial co2-production it might be possible to influence this negative impact. Recently, bioengineered bacteria have been shown to improve the efficiency of the fermentation process in producing ethanol from macroalgae, potentially overcoming one of the major barriers to using macroalgae for biofuel production[78] and supplying a renewable energy source. A pilot facility is under way in Chile, though the environmental impacts of the technology have not yet been assessed. The use of enzymes derived from marine organisms to enhance industrial processes can also bring about improvements in energy consumption.

Socioeconomic Aspects

Encouraging Forecasts

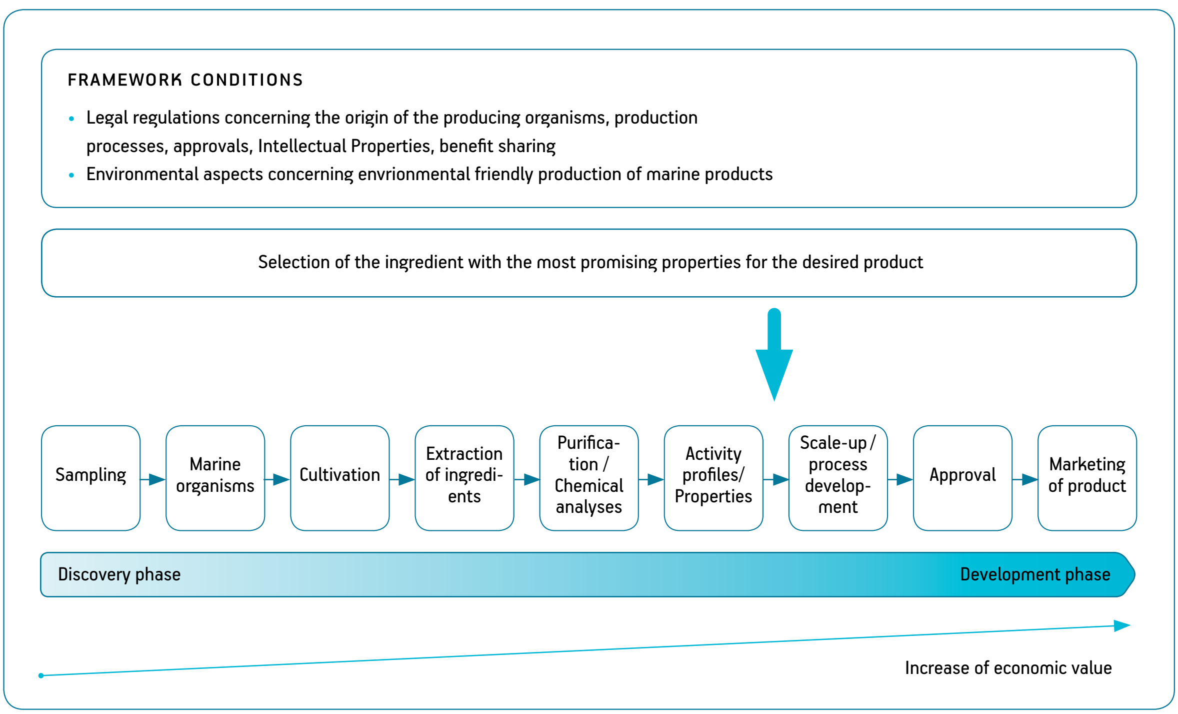
The global biotechnology revenues came to $ 84.5 billion in 2010 by analysis of 622 companies.[79] While Blue Biotechnology represents only a nascent and relatively small part of this market, given the vast untapped potential the marine biotech sector holds promising growth prospects for the future. The global market for marine biotechnology is forecast to reach $ 4.1 billion by 2015. The market for marine bioactive substances is forecast to register the fastest growth rate of more than 4 % during the period 2009–2015 and the marine biomaterials market was projected to reach $ 1.7 billion by 2012.[80]

Europe constitutes one of the largest markets for the marine biotechnology industry with about 27 % of the demand.[2] The Marine Board of the European Science Foundation estimates that Europe's segment of the Blue Biotechnology market amounts to € 2.8 billion ($ 3.5 billion) by with a future annual growth potential of 12 % assuming a strong cooperation of industry and science.[3] Furthermore, Baltic Sea countries contributed almost half of the European demand for marine biotechnology in 2011.[2]

This expected market growth is driven not only by the rise in interest from medical, pharmaceutical, aquaculture, nutraceutical and industrial sectors, with ever widening applications in many end-use areas (pull-effect). It is also "pushed" by the rapid increase in the inventory of marine natural products and genes of commercial interest derived from bioprospecting efforts. As a consequence, today an ever greater number of small companies exist with the specific focus of marketing marine compounds.

In terms of end-use, the healthcare industry constitutes the largest and fastest growing segment for marine biotechnology. The global market for marine-derived pharmaceuticals was valued at nearly $ 4.8

Figure 4: High-added value chain of the exploitation of marine organisms from the habitat to commercialisation of biotechnological product.



billion in 2011, $ 5.3 billion in 2012 and is projected to be worth nearly $ 8.6 billion by 2016, a compound annual growth rate of 12.5 % between 2011 and 2016.[81]

REGIONAL CASES

Blue Biotechnology: A Real Business

As the first important commercial company in the world with a clear emphasis on development of anti-cancer drugs from marine natural products, the Spanish company PharmaMar was founded in 1986. It has several marine drug candidates in the clinical trial pipeline. Yondelis® was derived from a tunicate and was the first product from PharmaMar in clinical use against special forms of cancer.[82] It is applied as drug for the treatment of soft tissue sarcomas, is supplied by Zeltia and had gross sales of € 72.2 million in 2010, a 70.3 % increase on 2009.[83]

Challenges and Cost Factors

The overarching challenge to marine biotechnology concerns the appropriation of marine resources, which are distributed within vast and complex ecosystems, while protecting and preserving marine resources for future generations.[84] Among key issues for Blue Biotechnology are the supply of organisms producing e.g. bioactive compounds, enzymes or fatty acids for biotechnological applications, the use of bioassays suitable for the desired field of application, the sustainable production of these ingredients, proper storage methods, sufficient technologies for scale-up and downstream processing as well as the development and the approval of the respective market product (figure 4). Downstream processing may cause up to 80 % of the production costs.[85] Table 9 displays the phases involved in the discovery and the development stages for marine derived products as well as the facilities required.

In the pharmaceutical field, one important bottleneck in the development of drugs is the great financial effort needed to carry out pre-clinical and clinical studies, required for ensuring the efficiency and safety of new drugs (approval). Furthermore compliance with legal regulations, which vary depending on the final application of the compound (for drugs, medical devices, cosmetics or food additives) have to be considered (see section on "Legal Aspects"). The consideration of these regulations before being able to bring a marine product to market is cost-intensive.

Table 9: Cost factors playing an important role in Blue Biotechnology.

Stage	Phase of biodiscovery / development	Procedures / methods	Laboratories / Equipment	Staff	Main cost factors (examples)
Discovery	Sampling	Collecting marine samples	Ships, remotely operated vehicles	Scientists, technicians	Financing the cruises
	Supply of new producer microorganisms or of metagenomic data sets , maintenance of culture collections	(i) microbiological methods (ii) genetic methods	(i) Laminar flows, autoclaves, incubation chambers, storage capacities for strain collection (-80°C, liquid nitrogen) (ii) S1 laboratories / thermalcyclers, sequencers, analytical software	(i) Microbiologists, biologists, technicians (ii) Geneticists, bioinformaticians, technicians	Staff salaries, purchase of equipment and laboratory materials
	Development of new cultivation – and/or genetic – based methods to stimulate production of known producer strains	Microbiological and/or genetic methods	See above + fermenters	See above	See above
	Extraction, structure elucidation, purification and storage of the valuable ingredients (e.g. as pure compound library)	Extraction procedures, chemical analyses	Laboratories following guidelines for chemical work, rotary evaporators, fraction collectors, HPLC, FCPC, MS, GC, NMR	Chemists, technicians	See above
	Screening panels with bioassays according to human, environmental and industrial needs	Cell-based test systems, enzymatic test systems	L2 laboratories, cell-culture laboratories, microplate readers for high-throughput	Microbiologists, cell biologists, pharmacists, agronomists, technicians	See above
Development	Sustainable supply of the valuable ingredients in sufficient amounts used for the marine products	(i) robust process development using fermentation procedures (ii) chemical synthesis (iii) genetic methods	(i) fermenters (250 L, 3,000 L and more) (ii) HPLC, FCPC, MS, GC, NMR (iii) S1 laboratories	Microbiologists, chemists, geneticists, engineers, technicians	See above
	Marine product development	Optimisation of the properties of the valuable ingredients according to product requirements, manufacturing using (bio) chemical methods, formulations	Equipment for chemical syntheses, software for structure-activity relationships	Chemists, medicinal chemists, pharmacists, biologists, technicians	See above

Stage	Phase of biodiscovery / development	Procedures / methods	Laboratories / Equipment	Staff	Main cost factors (examples)
Development	Ensuring Intellectual Property	Agreements and contracts with respect to benefit-sharing and joint ownership, patent applications	Offices	Patent lawyers, legal scholars	Costs for application and maintenance of the patents
	Approval of the marine product	Considering EU and national directives for the desired application	Laboratories according to Good Manufacturing Practice guidelines, national guidelines and EU directives	Staff with specific expertise in the desired application (e.g. medics, pharmacists, biologists, chemists, nutritionists)	Fulfil the requirements of the approval procedures (e.g. in case of drugs: clinical phases I, II, and III)
	Commercialisation of the marine product	Evaluation of market potential, development of marketing strategy	Marketing via internet, fairs, conferences, etc.	Business and marketing experts	Marketing costs including staff salaries, add campaigns, travel costs and product samples

Political Strategies

European Context

In Europe, the potential value of marine resources for Blue Biotechnology is only just beginning to be recognised at the political level (Figure 5). Already back in 2001, the European Science Foundation's (ESF) Marine Board Position Paper 4 "Marine Biotechnology – A European Strategy for Marine Biotechnology" had recognised the underexploited benefits of marine biotechnology in Europe and called for a European initiative to mobilise scattered human capital and refocus dispersed infrastructure. By 2009, the European Commission's Knowledge Based Bio-Economy Network (KBBE-NET) advocated for integrated marine biotechnology R&D in Europe and made the first attempt to map national research priorities in European countries. In 2010, ESF´s Marine Board updated their Position Paper "Marine Biotechnology: A New Vision and Strategy for Europe",[3] calling for a collaborative industry-academia approach to provide strategic assessment, identify priorities, analyse the socioeconomic context and provide policy recommendations. In 2011, the Internal Co-ordination Group for Biotechnology (ICGB) of the OECD stated that Blue Biotechnology has a considerable potential to address global challenges in population health, food security, industry and environmental sustainability as well as protecting and preserving marine resources for future generations.[84]

Despite these calls for strategic direction, to this day the EU still lacks a coherent marine biotechnology research and technology transfer policy. Instead, individual European countries support, to varying degrees, national and regional marine biotechnology initiatives and programmes based

Figure 5: Most important documents and activities from science and policy regarding marine biotechnology on the European level. (ESF = European Science Foundation, EC = European Commission, CWG-MB = Collaborative Working Group on Marine Biotechnology, R&D = Research and Development, OECD = Organisation for Economic Co-operation and Development, CSA MarineBiotech = Coordination and Support Action "MarineBiotech", ERA-NET = European Research Area Network, DG Mare = Directorate-General for Maritime Affairs and Fisheries, KBBE-NET = Knowledge Based Bio-Economy Network).

Year	Documents and activities
2001	ESF Marine Board Position Paper 4 "Marine Biotechnology: A European Strategy for Marine Biotechnology"
2006	EC background paper no. 10 on Marine Biotechnology (supplement to the Green Paper on Maritime Policy, 2006)
2008	• EC-US Task Force on Biotechnology Research (marine genomics) EC-US Task Force on Biotechnology Research (marine genomics) • EC communication "European Strategy for Marine and Maritime Research" highlights the need for research on marine biodiversity and biotechnology
2009	• CWG-MB report prepared for KBBE-NET advocating integrated Marine Biotech R&D in Europe
2010	• ESF Marine Board Position Paper 15 "Marine Biotechnology: A new Vision and Strategy in Europe" • OECD Working Party on Biotechnology initiated work on marine biotechnology • EurOCEAN 2010 Ostend Declaration „The Seas and Oceans are one of the Grand Challenges for the 21st century" identified priorities such as marine biotechnology among others
2011	• CSA MarineBiotech for ERA-NET on Marine Biotechnology starts • OECD highlights the opportunities of Marine Biotechnology to address global challenges • EC communication on Horizon 2020 identified marine resources for innovative applications
2012	• Blue Biotech Event in the frame of the EU INTERREG project SUBMARINER • Report „Blue Growth-Scenarios and Drivers for Sustainable Growth from the Oceans, Seas and Coasts" (on behalf of DG Mare) • EC communication identified Blue Biotechnology as one promising "Blue Growth Focus Area" that could deliver sustainable growth and jobs in blue economy • Rio+20 commitments address the sustainable use of marine biodiversity
2013	ERA-NET on Marine Biotechnology might start
2020	Marine Biotechnology will substantially meet objectives of the Europe 2020 strategy

on their own needs and priorities, resulting in a fragmented effort.

The EU currently provides about € 36 million to fund Blue Biotechnology initiatives through its 7th Research Framework Programme (2007–2013). Within this framework several projects focussing on the exploration of marine organisms have recently been selected, i.e. MaCumBa, PharmSea, BlueGenics and SeaBioTech and are expected to start by the turn of 2012 /2013.[86]

Even though this shows the growing interest of the EU in this field, the € 32 million committed still only represent a small fraction of the overall € 1.9 billion spent on food, agriculture and biotechnology initiatives. Also the rather short term cycles of project based funding do not correspond with the long-term processes required in the field of Blue Biotechnology. Rather than being able to pursue a specific research field over a longer time span and thus being able to build up the necessary expertise – researchers and research institutes often have to shift emphasis according to the given funding opportunities rather than the other way round.

Further strategic support is expected through the Blue Growth initiative recently launched by the European Commission's DG Mare, which will focus among other topics, on the use of marine resources in the pharmaceutical and cosmetic industries. Recently the communication of the European Commisssion "Blue Growth – opportunities for marine and maritime sustainable growth" emphasised that Blue Biotechnology is one of few Blue Growth Focus Areas with the potential for research and development to deliver technology improvements and innovation.[87] European support for Blue Biotechnology can also be found in the ERA (European Research Area)-NET in marine biotechnology preparation action by the CSA MarineBiotech project, which is currently scoping the content and shape of a transnational funding activity and beginning the work of securing commitment to the provision of funds.

Baltic Sea Region Context

In the Baltic Sea, Germany and Denmark, have recognised the potential of the Blue Biotechnology sector and its various applications.

GERMANY

In Germany, Schleswig-Holstein has been a pioneer in the Blue Biotechnology field, beginning back in 2003 with its "Current status and future perspectives of marine bioactive compounds" report provided by the former Technology Foundation of Schleswig-Holstein.[88] The state's government then started the initiative "Zukunft Meer – Sea our future" in 2004, which includes Blue Biotechnology as one of the promising topics. This led e.g. to the financial support of the Fraunhofer Research Institution for Marine Biotechnology EMB and to the foundation of the Kieler Wirkstoff-Zentrum (KiWiZ) at GEOMAR (Kiel Center for Marine Natural Products at GEOMAR), a research centre specifically focused on research and development of compounds from marine microorganisms for use in various applications.

DENMARK

In Denmark, the Ministry of Food, Agriculture and Fisheries has made efforts to set a strategic direction for the nation's Blue Biotechnology industry. Keeping in mind the specific competence of the various companies (9) and research institutes (>15) present in Denmark in this field as well as the potential economic benefits to be achieved, it suggested six priority areas of marine biotechnology[89]: increased exploitation of marine biomass, new farming operations, healthy diet, discovery of new compounds, materials and biological activities, extraction of valuable biochemical components and biofilms.

Elsewhere, Blue Biotechnology initiatives remain disjointed efforts or projects mainly driven by individual researchers and /or institutions. No cohesive strategic plan is available for the development of this sector in the Baltic Sea Region as a whole.

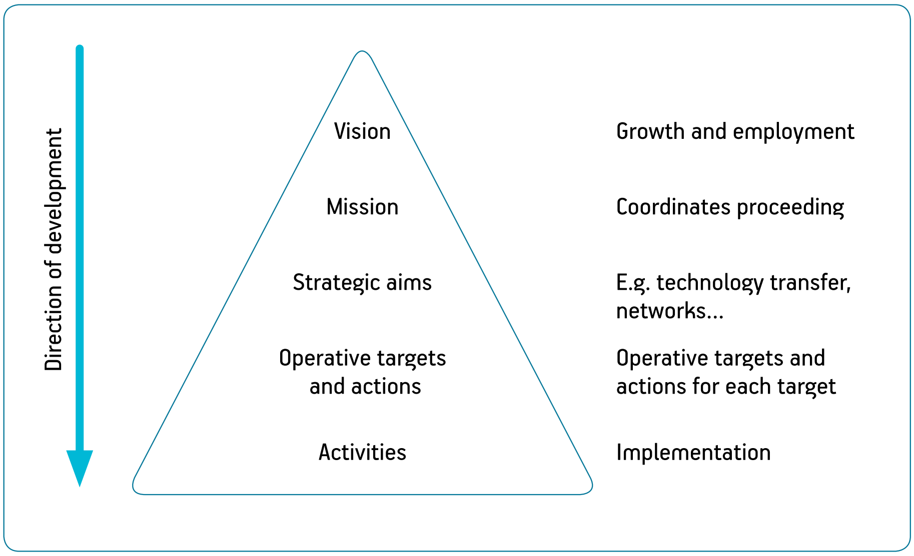
However, the basic elements on which to build such a strategy would already be in place. As shown, technologies necessary for bioprospecting of Baltic organisms are already established in some regions or countries, providing a good basis for technology transfer to other Baltic Sea countries. Furthermore local and international networks in the Baltic Sea Region that cover related fields such as life sciences or biotechnology (e.g. Life Science Nord, ScanBalt) already provide a good basis for promoting the Blue Biotechnology sector.

REGIONAL CASES

A Model for the Region?

The "Masterplan Marine Biotechnology Schleswig-Holstein – a regional development strategy" will be implemented in 2013 and will provide a path to the long-term strategic development of marine biotechnology in the state. The promising potential of marine biotechnology will be explored economically in a sustainable manner, through systematic knowledge and technology transfer and should lead to the generation of growth and employment in Schleswig-Holstein. This could serve as model for other countries and the Baltic Sea Region as a whole.

Figure 6: Structure of the Masterplan.



Legal Aspects

The process from research and development to marketing of a product from marine resources involves many single steps, which are strongly linked to ensure the protection of the environment, the Intellectual Property protection of all collaborators and the safety for the consumers using the marine product. Therefore it is necessary to consider various laws, guidelines and agreements. Some of the most important ones are given in following section to give an impression about the complexity of regulations.

Environmental and Species Protection

The Convention of Biological Diversity (CBD) has four objectives the conservation of biological diversity, the sustainable use of the components of biological diversity and the fair and equitable sharing of benefits arising out of the utilisation of genetic resources. The Microorganisms Sustainable Use and Access Regulation International Code of Conduct (MOSAICC) is a voluntary code of conduct drafted by worldwide partners from both commercial and not-for-profit sectors which serves as a tool to support the implementation of the CBD at the microbial level in accordance with relevant rules of international and national laws.

It is worth noting that European legislation is also in place concerning environmental liability. The directive 2008/56/EC of the European Parliament and of the Council address at establishing a framework for community action in the field of marine environmental policy (Marine Strategy Framework Directive). This pillar of the of the European maritime policy stated "…Member states shall take the necessary measures to achieve or maintain good environmental status in the marine environment by the year 2020 at last." Further regulations focus on the prevention and remedying of environmental damage (2004/35/CE) as well as the deliberate release into the environment of genetically modified organisms, in case this is desired, as for instance for the degradation of pollutants (2001/18/EC).

Intellectual Property

The application for a patent is necessary to safeguard the exploitation rights of a new marine product with commercial potential. The European Patent Convention (EPC) provides an autonomous legal system for the granting of European patents via a single, harmonised procedure before the European Patent Office (EPO). The EPC is linked and interfaces with the national patent laws of the EPO member states. Generally, the European patent is subject to the same conditions as a national patent granted by that country. All Baltic countries have developed and adopted patent protection laws into their national legislation.

Concerning the ownership of patents arising from multinational collaborative projects, European Intellectual Property Rights regulations ensure that jointly generated Intellectual Property is also jointly owned (following share assignments previously agreed by the joint owners) and that rules are set for protection, use, licensing, cost and profit sharing and territorial division of patent protection and exploitation markets.

Safety and Good Manufacturing Practices

Safety regulations concerning the approval for the specific application of a marine product have to be taken into account before it can put in the open market. European directive 2004/10/EC provides principles of good laboratory practice that must be applied to the non-clinical safety testing of items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs, food and feed additives and industrial chemicals.

In the case of drugs for humans and veterinary drugs the approval of the responsible higher federal authority or the permission of the European Commission is necessary (according to the guidelines of Good Manufacturing Practice and regulations such as 2003/94/EC, 91/412/EEC, 726/2004/EC, 1901/2006/EC, 1768/92/EEC, 2001/20/EC, 2001/83/EC, 726/2004/EC and 1394/2007/EC or 90/385/EEC, 93/68/EEC, 93/42/EEC, 2001/104/EC and 98/79/EC for the marketing of medical devices).

In the case of food additives, under European legislation, these must be authorised before they can be used in foods. The authorisation is granted following safety assessments carried out by the European Food Safety Authority, which provides independent scientific review. EU legislation consists of a framework directive covering additives in general (89/107/EEC) as well as directives for colouring (94/36/EC), sweeteners (94/35/EC), other food additives (95/2/EC), food enzymes (1332/2008/EC) and other directives pertaining to approved purity criteria.

Suppliers wishing to place cosmetic products on the EU market must comply with the EU cosmetics directive 76/768/EEC. Among the main requirements are a safety assessment of the finished cosmetic product and the availability of the product information file. The directives 2001/36/EC and 98/8/EC concern the placing of plant protection products and biocidal products, respectively, on the market.

SWOT Analysis

STRENGTHS	WEAKNESSES
• Enormous potential for growth, with many Baltic micro – and macroorganisms already used for market products or showing great potential for high-value applications • Technologies necessary for bioprospecting of Baltic organisms are already established in some regions or countries, providing a good basis for technology transfer to other Baltic Sea countries • Existing local and international networks in the Baltic Sea Region that cover related fields such as life sciences or biotechnology (e.g. Life Science Nord, ScanBalt) provide a good basis for promoting the Blue Biotechnology sector • Successful commercial case studies in the Baltic Sea Region are already available • Internationally well-known scientists are already working in specific fields of Blue Biotechnology in single regions of the Baltic Sea. These scientists could be promotors for technology and knowledge transfer for enhancing activities in Blue Biotechnology in their own but also in other Baltic countries.	• Low awareness in most Baltic Sea Region countries about the economic and scientific potential of Blue biotechnology • Skills shortage, especially in the cross-cutting disciplines necessary for development of high-value products from Baltic Sea organisms • Limited number of financially strong companies in the Baltic Sea Region • Challenging framework for the foundation of new companies (legal regulations, financial support, high taxes) • Low technology transfer, low networking activities and low collaborative activities in the Baltic Sea Region concerning Blue Biotechnology • Low readiness or aptness of the companies to invest in R&D in some Baltic Sea Region countries • Limited readiness of venture capitalists to invest in young start-up's • Limited skills and finances in sales and marketing within the companies that have already developed products of Baltic Sea origin • Limited knowledge on the scale of environmental impacts, in particular arising from the release of bioengineered compounds into the marine environment.
OPPORTUNITIES	**THREATS**
• Universities have high activities in R&D with a lot of innovative, application-oriented projects, highly encouraged scientists and modern, well equipped facilities so that innovative products can constantly be expected in the near future • Companies are constantly searching for new and innovative ideas to fulfil customer needs • Growing interest in marine biotechnology as a potential source for greener and smarter economies • Growing market of the cosmetics industry	• Lack of a coherent EU marine biotechnology research and technology transfer policy • Lack of policies supporting biotechnology in some Baltic Sea Region countries • Lack of financial support due to the current economic and financial crisis • Short term project funding cycles of public funding programmes not suitable for long term processes • Lack of public support for the field in general

OPPORTUNITIES	THREATS
• Growing EU support in the form of the EU Blue Growth initiative under Integrated Maritime Policy and structural funds • Growing EU support in the frame of Horizon 2020 and BSR programmes • Growing support by investors • Participation at the ERA-NET • Continuous development of new advanced technologies • Growing public demand for natural products in the food, cosmetics and pharmaceutical industries • Public look upon Baltic Sea Region brand products positively	• Lack of public private partnerships, insufficient commercialisation skills, know-how and support at regional and national levels.

Knowledge Gaps

An important point in the field of Blue Biotechnology is the need to determine the best strategy to ensure the transfer of biotechnology research results to commercial products and to close the financial gap between the discovery or idea generation and the commercial application. Especially meeting the industrial requirements regarding the supply of the compound or material used in sufficiently high amounts and high quality for the desired product is an important key issue. Techniques and the knowledge in process-development necessary for scale-up the production are usually not available in the laboratories where the discovery comes from. By means of the amount of publications it can be shown that research in marine early drug development is tremendous. Nevertheless only few compounds have entered the pharmaceutical pipeline till now. One reason is the lack of interest from industry, because the new compounds are usually not patented but published by the scientists. A strong cooperation between the research institutions, industrial partners, experts in ensuring Intellectual Properties and technology transfer, with the aim of patenting and publishing without time-gap should lead to a mutual agreement of the involved partners. In case industrial partners show interest in the further development of results from the discovery stage, the need for signing contracts concerning applications for patents as well as patent valorisation between the contributing parties might hinder the product development, because of conflicting interests. By means of the amount of publications it can be shown that research in marine early drug development is tremendous. Nevertheless only few compounds have entered the pharmaceutical pipeline till now. One reason is the lack of interest from industry, because the new compounds are not patented but published the scientists. A strong cooperation between the research institutions, industrial partners, experts in ensuring Intellectual Properties and technology transfer, with the aim of patenting and publishing without time-gap should lead to a mutual agreement of the involved partners. In case of product development by the discoverers themselves there might be a problem, because know-how about marketing is missing.

It is also important to find ways to the sustainable management of scientific results so that the knowledge generated by research projects can be made easily accessible once the projects have ended.

On the scientific level several key issues exist. Among them are e.g. the need for more knowledge about the stimulation of the production of bioactive compounds and other valuable ingredients with the aim to enhance the amount but also to enhance the probability of success in finding new ingredients by cultivation-based approaches. In case of handling metagenomic data from marine samples more knowledge about transferring and expression of genes containing the information for possible new compounds or enzymes using sufficient cell-systems is an urgent demand.

Multiple other knowledge gaps also exist at the application level. For example, further research is needed on the impact on marine habitats and species of releasing bioengineered compounds and bacteria into the marine environment or on the impact of using bioengineered bacteria to optimise the fermentation process in the production of ethanol from micro – or macroalgae.

Conclusions

Even if the Blue Biotechnology field is still very much research and development focused and still shows a limited economic performance today, numerous forecasts project major growth, huge demand and correspondingly large markets.

In the Baltic Sea Region Blue Biotechnology has thus far not played a major role. However, here too it has great potential for wide implementation, based on the given expertise as well as equipment present already by now for biotechnology in general, which merely has to be put to use for the exploration from marine organisms. What is more: the Baltic Sea Region shows a great tradition in not only developing but also pursuing transnational cooperative strategies, which is a core requirement identified in this chapter for turning Blue Biotechnology research into real life applications. Based on such strategy regional disparities might also be turned into advantages, using laboratories in the new Eastern Baltic Sea countries while developing close links with the big pharmaceutical industry based more in the Western Baltic Sea region. Amplified coordination between potential contributing partners in the region would have substantial positive effects on scientific productivity, international success, foundation of new companies and growth of existing companies, financial support of investors, employment and most importantly contribute towards improved human health and environmental conditions of the Baltic Sea.

What is needed is a Baltic Sea wide strategy for the implementation of Blue Biotechnology around the Baltic Sea which is aligned with EU level developments. The strategy should be based on national action plans which take into account the respective strength of institutions and experts in the given country while also responding to most urgent market needs. Based on such a strategy a sequence of transnational priority actions could be initiated such as the establishment of a "Baltic Sea Region Blue Biotechnology Network", a centre for bioprospecting of Baltic Sea microorganisms or a distribution network for cosmetics, health care and wellness products using a Baltic Sea Region label, the scaling up of marine genomics as a source of novel enzymes from the Baltic Sea or the advancement of innovative marine technologies stemming from the region.

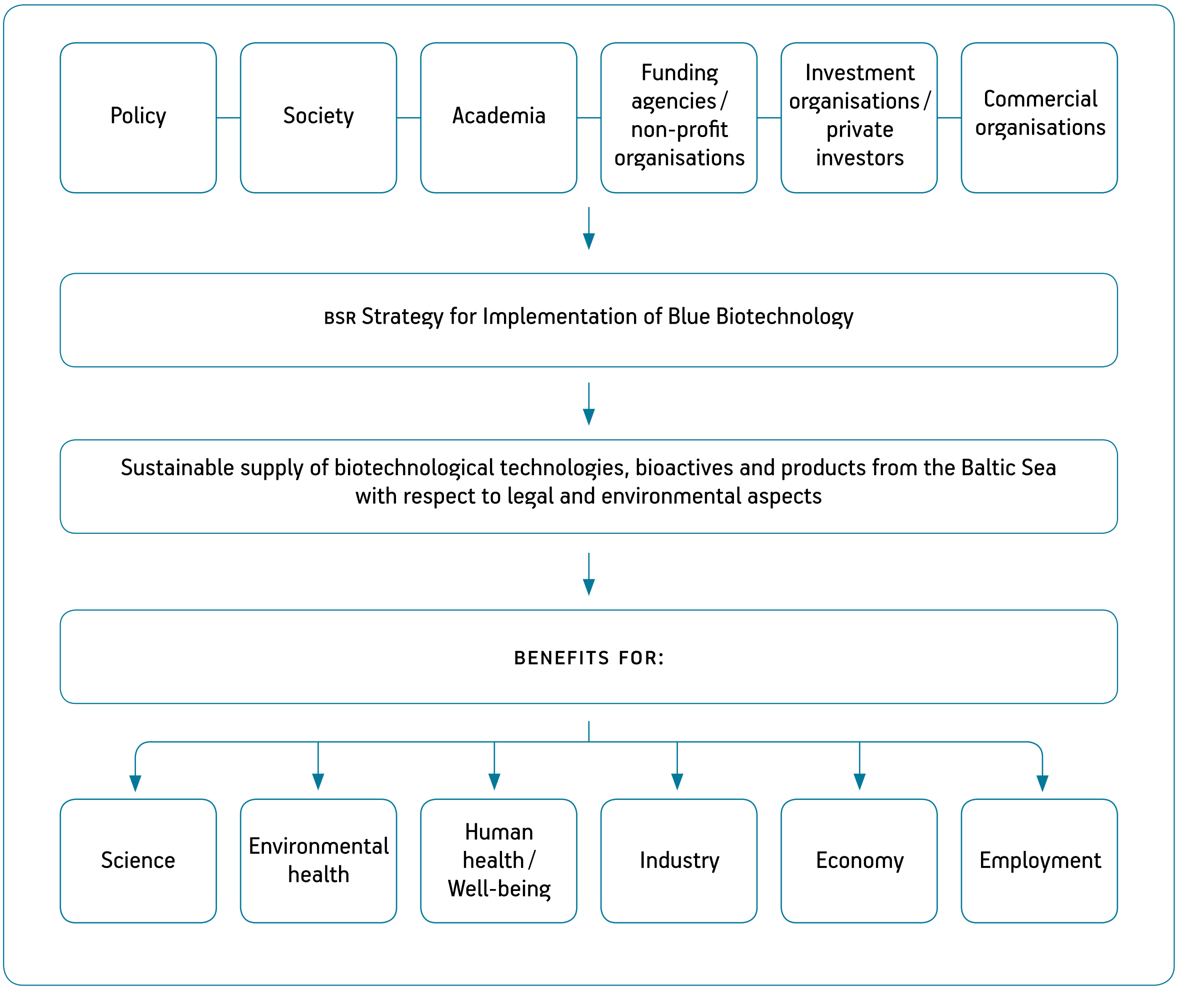
Concerted action of all contributing actors would lead to a strategy providing future perspectives and benefits for the whole Baltic Sea Region (figure 7).

Recommendations

A strategy for implementation of Blue Biotechnology within the Baltic Sea Region should include the following critical topics:

- Coordinative activities between society, policy, academia, commercial organisations, funding agencies, investment organisations and private investors are necessary to develop a strategy for successful technology transfer of scientific results to biotechnological applications

Figure 7: Wider implementation of Blue Biotechnology within the Baltic Sea Region could contribute to meet the great challenges of the 21st century.



- The strategy for enhancing activities in Blue Biotechnology should consider EU initiatives, such as the ERA-NET
- Funding by the EU within the frame of Horizon 2020 and Baltic Sea Region programmes should support the implementation of Blue Biotechnology by financing e.g. pilot plants
- All Baltic Sea Region countries have to improve their collaborative efforts and the coordination between research institutions and industry
- Blue Biotechnology roadmaps with special emphasis on regional and national key issues and topics that can only be realised in cooperation with other Baltic Sea Region countries would be a helpful tool for science, industry, politics and stakeholders
- The implementation and growth of activities in the field of Blue Biotechnology in the Baltic Sea Region would be strongly supported by the establishment of a "Baltic Sea Region Blue Biotechnology Network". Existing networks covering the fields of life science or biotechnology in general could effectively contribute to the new network, which would focus exclusively on the exploration of marine sources