A new network for the advancement of marine biotechnology in Europe and beyond

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A new network for the advancement of marine biotechnology in Europe and beyond

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The authors declare a potential conflict of interest and state it below

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contribution statement

AR designed the article concept and drafted the manuscript. All authors read, commented, improved and approved of the final version of the manuscript.

Keywords

marine biotechnology, Marine Natural Products, Blue growth, marine biodiversity and chemodiversity, Responsible Research & Innovation, stakeholder engagement, science communicaion, sustainability

Abstract

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Marine organisms produce a vast diversity of metabolites with biological activities useful for humans, e.g. cytotoxic, antioxidant, anti-microbial, insecticidal, herbicidal, anticancer, pro-osteogenic and pro-regenerative, analgesic, anti-inflammatory, anti-coagulant, cholesterol-lowering, nutritional, photoprotective, horticultural or other beneficial properties. These metabolites could help satisfy the increasing demand for alternative sources of nutraceuticals, pharmaceuticals, cosmeceuticals, food, feed, and novel bio-based products. In addition, marine biomass itself can serve as the source material for the production of various bulk commodities (e.g. biofuels, bioplastics, biomaterials). The sustainable exploitation of marine bio-resources and the development of biomolecules and polymers are also known as the growing field of marine biotechnology. Up to now, over 35,000 natural products have been characterized from marine organisms, but many more are yet to be uncovered, as the vast diversity of biota in the marine systems remains largely unexplored. Since marine biotechnology is still in its infancy, there is a need to create effective, operational, inclusive, sustainable, transnational and transdisciplinary networks with a serious and ambitious commitment for knowledge transfer, training provision, dissemination of best practices and identification of the emerging technological trends through science communication activities. A collaborative (net)work is today compelling to provide innovative solutions and products that can be commercialized to contribute to the circular bioeconomy. This perspective article highlights the importance of establishing such collaborative frameworks using the example of Ocean4Biotech, an Action within the European Cooperation in Science and Technology (COST) that connects all and any stakeholders with an interest in marine biotechnology in Europe and beyond.

Contribution to the field

Dear colleagues, The co-authors (Rotter et al.) are are submitting a perspective article with the general aim of highlighting the emerging importance of this exciting field of marine biotechnology. This field is an excellent example of how science and innovation collaborations should be conducted nowadays as science is rapidly evolving, not only in terms of scientific content but also in its mode of conduct. Interdisciplinary (and even transdisciplinary) teams are today mandatory, and, on top of that, and research and innovation development must include industrial policy making and general public representatives. This is especially true in newer fields such as marine biotechnology. This perspective article highlights the importance of all mentioned partners to bridge the communication gap between science-industry-society (the latter including policy makers and general public). Only the inclusion of all relevant actors can guarantee an innovative and sustainable society. One of the few inclusive, transdisciplinary and participatory network is a recently established COST Action »European transdisciplinary networking platform for marine biotechnology« (Ocean4Biotech), joining together all interested actors from the marine biotechnology field, from biological, chemical experts, to experts in communication, ethics and Responsible Research and Innovation.

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Keywords: marine biotechnology, marine natural products, blue growth, marine biodiversity and chemodiversity, responsible research and innovation, stakeholder engagement, science communication, sustainability.

Abstract

Marine organisms produce a vast diversity of metabolites with biological activities useful for humans, e.g. cytotoxic, antioxidant, anti-microbial, insecticidal, herbicidal, anticancer, pro-osteogenic and pro-regenerative, analgesic, anti-inflammatory, anti-coagulant, cholesterol-lowering, nutritional, photoprotective, horticultural or other beneficial properties. These metabolites could help satisfy the increasing demand for alternative sources of nutraceuticals, pharmaceuticals, cosmeceuticals, food, feed, and novel bio-based products. In addition, marine biomass itself can serve as the source material for the production of various bulk commodities (e.g. biofuels, bioplastics, biomaterials). The sustainable exploitation of marine bio-resources and the development of biomolecules and polymers are also known as the growing field of marine biotechnology. Up to now, over 35,000 natural products have been characterized from marine organisms, but many more are yet to be uncovered, as the vast diversity of biota in the marine systems remains largely

unexplored. Since marine biotechnology is still in its infancy, there is a need to create effective, operational, inclusive, sustainable, transnational and transdisciplinary networks with a serious and ambitious commitment for knowledge transfer, training provision, dissemination of best practices and identification of the emerging technological trends through science communication activities. A collaborative (net)work is today compelling to provide innovative solutions and products that can be commercialized to contribute to the circular bioeconomy. This perspective article highlights the importance of establishing such collaborative frameworks using the example of Ocean4Biotech, an Action within the European Cooperation in Science and Technology (COST) that connects all and any stakeholders with an interest in marine biotechnology in Europe and beyond.

Introduction

During four billion years of evolution in the ocean, marine organisms have evolved in their environment to biosynthesize a plethora of biopolymers and biomolecules. These include the unique secondary metabolites that are produced in response to environmental stimuli. They play important biological roles in improving competitiveness, providing chemical defense against predators or competitors and facilitating reproductive processes. These biomolecules are not always essential for the growth and development of the organism, but they are important for the survival and well-being in its environment. Furthermore, some compounds such as marine enzymes have properties essential for industrial applications like thermostability or tolerance to a diverse range of pH and salinity conditions. These properties are being utilized in various industries such as in the food, animal feed, leather, textile and horticulture industries, and in bioconversion and bioremediation processes (Rao et al., 2017). Marine biotechnology appeared in the 1960s and 1970s when scientists realized the potential of living organisms and their natural products for industrial exploitation (Dias et al., 2012). Initially, the investigation of marine ecosystems relied on the easily accessible organisms like corals and sponges as well as macroalgae that have high biomass levels and were representative of targeted ecosystems (Greco and Cinquegrani, 2016). Therefore, most of the known natural products deriving from the marine environment were initially isolated from macro-organisms. On realizing that marine microbial biodiversity is vast, largely underexplored and unexploited, the application of marine microbial biotechnology aiming to valorize marine resources is a natural step forward in the development of the biotechnology sector.

For a long time, it has been considered that only around 1% of the whole marine microbial population could be cultured under laboratory conditions (Vartoukian et al., 2010). However, recent findings suggest the percentage of culturable microbial population is higher; an estimated 13% - 78% of genera are cultured, depending on the environment (Lloyd et al., 2018). For example, environments with high human engagement and disease-driven research benefit from greater culturing effort (Steen et al., 2019; Lloyd et al., 2018). Since many cells in nonhuman environments belong to novel phyla, new culturing approaches and innovations will increase the percentage of uncultured microbes (Steen et al., 2019). Culture-independent methods using omics approaches are nowadays used to detect microorganisms that are yet uncultured. These methods include high-throughput sequencing, metagenomics, transcriptomics, proteomics, metabolomics and bioinformatics resources for the identification of organisms and elucidation of metabolic pathways responsible for production of chemical compounds, as well as DNA-based or heterologous expression systems. Microbial identification is only an initial step and additional research is essential to develop cultivation techniques to obtain the necessary biomass in a sustainable manner. Next, biochemical and genetic engineering methods are required for the production of high quantities and quality of proteins, marine oils and other secondary metabolites of interest. Figure 1 provides a schematic representation of parameters that should be considered for the whole bioprospecting process, starting from the selection of marine organisms, for their cultivation prior to their utilization for the biosynthesis of high-value bio-components and for investigation of their biological potential in various industries.

Natural products are currently the most common source of therapeutic agents. The World Health Organization estimates that approximately 80% of the world's population uses remedies based on natural products to treat their basic health problems. Over 35,000 bioactive compounds have been isolated and chemically characterized from marine organisms since the 1960s (Lindequist, 2016). While before 1985 less than 100 natural products were discovered annually, in the late 1990s, this number rose to over 500 new products discovered yearly up to over 1,000 since 2008, mainly due to the advances in analytical methods (Carroll et al., 2019; Lindequist, 2016). The application of new dereplication strategies using mass spectrometry (MS) and the use of high-resolution Nuclear Magnetic Resonance (NMR) spectrometers with cryoprobes have enabled the discovery of new natural products even at the nanomole scale (Klitgaard et al., 2014). The most common approach used for the discovery of new marine bioactive chemical entities involves the screening of crude extracts or partially purified fractions of similar polarities against selected test organisms or therapeutic targets, followed by the purification and the structure elucidation of the active ingredients. The purification of metabolites is usually performed by means of chromatographic separation techniques combined with high-resolution MS based approaches that allow a rapid and accurate identification of the molecular mass and formulae of bioactive compounds. These methods are becoming a gold standard for the rapid and reliable dereplication of natural product extracts or fractions (Gaudêncio and Pereira, 2015).

The unique structural architecture and broad range of activities exhibited by marine metabolites have caught the attention of the scientific community. This has resulted in the development of research programs promoting innovation and industrial uptake along with the creation of new jobs and of a competitive environment for biotechnology-oriented enterprises as stated in the Blue Growth Strategy of the European Union (EU). This orientation is in line with the strategy for "A sustainable bioeconomy for Europe: strengthening the connection between economy, society and environment" which is a 2018 update from the original 2012 Bioeconomy Strategy by the European Commission (EC). The strategy aims to create a more innovative, resource-efficient and competitive society that will reconcile drug discovery and food security with the sustainable and economically viable use of renewable resources for industrial purposes while ensuring environmental protection.

Prerequisites for marine biotechnology (Figure 2)

Sustainability. There are two sustainability levels that must be considered to effectively implement marine biotechnology in practice: (i) environmental and (ii) supply sustainability. (i) Environmental sustainability tackles the main sources of marine biomass which come either from species harvested in nature or from those that can be cultivated. It is especially relevant when wild stocks are the only source of supply and they are over-harvested, or where targeted marine species are rare, in the deep, or difficult to re-sample. The harvesting/sourcing of any target species should thus not threaten marine biodiversity and the future availability of target species. To minimize the environmental impact, the biotechnology community should consider valorizing side and waste streams and co-products, target sustainably cultured marine organisms and those that are sufficiently productive to supply specific high added-value biomolecules. (ii) Sustainable supply of biomolecules represents key bottlenecks, as they are usually present in trace amounts. To guarantee a sustainable sourcing and production of target compounds, biologically active molecules or whole organisms should therefore be considered in a life cycle assessment and a multi-risk environmental analysis context. This will attain a global evaluation including environmental, health and economic aspects for both the biological (sourcing) and technical (supplying) cycle. Industrial symbiosis and circular economy approaches must therefore be applied to find sustainable ways for utilization of marine bioresources (blue growth) using green production techniques that economize on exhaustible resources (green growth, Rodrik, 2014).

Industry. Marine biotechnology generates various products and services, from the production of biofuels, food, feedstuffs and products for use in agriculture (high-volume, low-value and low-risk products), to the discovery of new biomaterials, cosmetics, nutraceuticals and pharmaceuticals (low-volume, high-value and high-risk products). Research and development investments for the discovery of marine-derived drugs entail high levels of capital expenditure and risk tolerance, as they require the use of state-of-the-art infrastructures and many years of basic and applied research. Despite some limitations, there are successful examples, as to date there are ten approved drugs, one example being trabectedin (ET-743), a product isolated from a Caribbean sea squirt *Ecteinascidia turbinata*, which is used for the treatment of advanced soft tissue sarcoma. This product first reached the market in 2007, after 20 years of research (Cuevas and Francesch, 2009). In practice, out of every 2,500 analogs from the marine environment that enter preclinical testing, only one may be safe and effective enough to reach clinical use (Gerwick and Fenner, 2013). There is a collaboration and communication gap between raw ideas and materials and their potential laboratory innovation and commercialization (Datta et al., 2014). This is being tackled by adopting three different strategies. (i) Firstly, by stimulating public-private partnerships in consortia that apply for research and innovation funding (such as Horizon 2020 and Horizon Europe, Europe's biggest research and innovation funding resource). (ii) Another alternative are the business incubators (such as Rocket57 in Northern Europe[1]), think tanks or stakeholder events that are often regionally financed to answer strategic regional developmental priorities and present a contact point for joining researchers, small and medium enterprises, industrial representatives and investors. (iii) Financial stimulation of networking activities (the example of COST Action Ocean4Biotech is presented in the next chapter of this article). The global marine biotechnology market is expected to reach ~$6.4 billion by 2025[2] and it currently represents only ~1% of the whole biotechnology market. Noteworthy, the oceans cover over 70% of the Earth's surface and contain an estimated 25% of the world's species (Mora et al., 2011), of which most are unknown and undervalorized. Hence, the marine biotechnology market is expected to expand at a much higher pace when high-throughput techniques and the collaboration between industry, science, general public and policy makers will be routinely used. The predominant players in the European marine biotechnology consist of some 140 micro SMEs (estimated by Ecorys in 2014) and academia that lack the financial stability necessary for sustained and long-term cutting-edge research.

Scientific community. To fully explore the ocean and its biota, the current screening and/or cultivation approaches of marine organisms of interest for biotechnological applications need to be optimized. High-throughput techniques produce vast amounts of data and can uncover the biodiversity and the metabolic potential of marine organisms. Hence, knowledge on data management, processing and data analysis to maximize the quality and quantity of resulting information needs to be advanced. Experts from the field of statistics, bioinformatics and chemometrics are essential in biotechnology research groups nowadays and their pipelines and

[1] https://rocket57.co/en/

[2] https://www.smithers.com/resources/2015/oct/global-market-for-marine-biotechnology

databases should be integrated, harmonized and publicly available to prevent duplication of efforts, reduce the overall costs and support the discovery process.

General public. While the world population is rising and is expected to reach over 8.5 billion by 2030, bioresources and available areas for cultivation and manufacture are declining. Hence, there is a growing demand for additional sources of food, drugs and chemicals. Marine biotechnology has the potential to mitigate these needs both by increasing the current production and by introducing new products in the food, feed, pharmaceutical, nutraceutical, healthcare, welfare, biomaterials and energy sectors. Nowadays, consumers expect innovative, efficient, safe, sustainable, ethical, financially and environmentally friendly solutions. We need to raise public awareness and improve communication to a broad audience regarding the benefits of marine biotechnology products to gain consumers' interest in eco-friendly products that meet high standards of sustainability.

Policy makers. Some national, regional and global strategies and guidelines are already in place to recommend investment into marine biotechnology and stimulate networking and transdisciplinary collaboration at the international level. These include the United Nations (UN) sustainable development goals[3], national and EU legislation that must be developed and harmonized. The UN Convention on the Law of the Sea[4] sets the rules for the exploitation, conservation and management of living marine resources. The Nagoya Protocol on Access to Genetic Resources and Benefit Sharing provides a legal framework aimed at creating transparency for those interested in the production and exploitation of genetic materials. Marine biotechnology development needs also to comply with the Habitats Directive (92/43/EEC) on the conservation of natural habitats and of wild fauna and flora, the Marine Strategy Framework Directive (MSFD) (2008/56/EC, CD 2017/848) establishing a framework for community action in the field of marine environmental policy, the EU Water Framework Directive – WFD (Directive 2000/60/EC), and the Maritime Spatial Planning Directive (2014/89/EU) for the planning of multiple uses of the maritime and coastal areas. Biomolecules and their production processes must also comply with specific regulations related to the targeted application (e.g. EU 2015/2283 Novel Foods and Ingredients, EC No 1223/2009 Cosmetic Regulation, EC No 1924/2006 Nutrition and Health Claims, EC No 1907/2006 REACH Regulation, among others). The widespread acceptance and certification of these novel compounds is a rigorous and time-consuming process where legislative documentation might need updating as novel compounds are being identified. It is thus necessary to encourage collaboration among scientists and policy makers, as outlined during the UNESCO High-Level Conference on the Ocean Decade (2018). Moreover, intellectual property strategies need to be established and agreed upon to conduct research in accordance with ethical recommendations for bioprospecting in the open ocean and beyond the national jurisdictions covered by the Nagoya protocol.

The establishment of a collaborative network as a solution for advancing marine biotechnology: COST Action Ocean4Biotech

Efficient and sustainable exploitation of the ocean's potential is possible only if industrial actors, researchers, the general public, policy makers and environmental experts work together. This direct interaction among different stakeholders across different countries is not always possible and limited programs have been supported until today that allow a minimal direct transdisciplinary interaction (see more in Supplementary Table S1).

[3] https://sustainabledevelopment.un.org/

[4] https://www.un.org/depts/los/convention_agreements/texts/unclos/unclos_e.pdf

From this viewpoint, the EU COST program that was established in 1971 represents an excellent opportunity for the creation of research networks on diverse topics, called COST Actions. These networks offer an open space for collaboration among stakeholders across Europe (and beyond), thereby catalyzing research advancement and innovation[5]. One of the recently approved Actions is CA18238 – European transdisciplinary networking platform for marine biotechnology (Ocean4Biotech)[6]. The motivation behind creation of this network is included in the SWOT analysis (see Supplementary Table S2 and the discussion therein). Ocean4Biotech is an international, unique and inclusive network that gathers experts from transdisciplinary fields of exact and natural sciences, social sciences and humanities, giving the Action participants the opportunity to work together and share their experiences creating a spill-over effect to foster marine biotechnology and bioeconomy in a sustainable way. Ocean4Biotech will apply the Responsible Research and Innovation Roadmap (Theodotou Schneider, 2019) involving scientists, citizens, policy makers and industry in the co-creation of knowledge and in the establishment of sustainable collaborative networks.

Notably, Ocean4Biotech builds upon existing knowledge from current and past projects and initiatives (see Supplementary Table S1). It aims to establish strong collaborations to avoid the duplication of efforts. The difference between Ocean4Biotech and the current and past efforts is this Action is envisaged as a "connecting-the-dots" funnel initiative that will gather scientists and professionals from all areas related to the marine biotechnology field. This enables a wider approach aiming to facilitate the circular economy in the marine biotechnology sector. Researchers from all fields and levels of expertise relevant to marine biotechnology will have the opportunity to participate in the Action and will be included in knowledge exchange activities (between the scientific fields as well as within, e.g. senior-to-junior knowledge transfer), establishing new collaborations and having an opportunity for career advancement. The developments from this COST Action can impact the industrial sector, and in turn will most likely influence governance boards. However, the efforts of Ocean4Biotech to establish connections between its members and linkages with other initiatives will not be possible without proactive science communication, extensive dissemination along with active engagement and outreach activities. Efficient communication will enable informing on the activities and objectives of the Action and will attract researchers to prepare and initiate new collaborations that will span beyond the lifetime of Ocean4Biotech.

How will Ocean4Biotech foster advances in the field of marine biotechnology?

There are five general objectives within the Ocean4Biotech COST Action:

1. **Description of marine biodiversity**. Knowledge of marine biodiversity is still limited. Moreover, there is a large interregional variability in species distribution and in their taxonomic knowledge. The lack of experts in marine species taxonomy, duplicates/redundancies/inconsistencies in the primary nucleotide databases, lack of type species and polyphyly of traditionally established taxa result in many misidentified or unidentified species/strains (many of which hold great potential for biotechnological applications). These are also important challenges to marine natural product programs. Hence, human resources, research effort, time and cost-efficient methods are needed to overcome the current gap in knowledge on biological and chemical diversity in marine ecosystems. These may be addressed by high-throughput methods that facilitate the discovery, classification and supply of organisms. However, high-throughput methods for biodiversity monitoring have not been routinely adopted and the methodology for biodiscovery is often not standardized. In fact,

[5] https://www.cost.eu/who-we-are/about-cost/

[6] https://ocean4biotech.eu

bioinformatics pipelines and big data analyses are changing the landscape for marine biotechnology, as around 18,000 new species are uncovered yearly[7]. Ocean4Biotech will propose operating procedures for uncovering the biodiversity using high-throughput methods, such as DNA barcoding approaches (Leese et al., 2016). These methods can then be combined with a more quantitative assessment by *in situ* hybridization techniques that allow the quantification and localization of specific microbial clusters within the environmental matrices. Such biodiversity assessment provides crucial information for subsequent monitoring and exploitation of marine organisms. The environmental impacts of such biological prospecting are considered minimal at the early stages of sampling, where the size of samples collected is small. Moreover, the standardization of the biodiscovery process is necessary as chemodiversity, even in the same taxa, greatly varies along geographical and environmental gradients, as well as seasonally and timely along the life cycle of organisms.

2. **Natural product discovery** is a process involving separation techniques in parallel with biological screening, followed by structure elucidation of the pure bioactive metabolites. If the target compound from a given species shows biotechnological potential, scale-up production and supply will certainly increase the environmental impact. However, the organic synthesis of the compound (although time-consuming and expensive) and/or production of the compound of interest using biological synthesis generally overcome the need for repeated collection and over-exploitation of the natural ecosystem. Therefore, Ocean4Biotech will build a compendium of pipelines, i.e. methods and procedures, detailed on a case study basis, starting from the creation of marine biorepositories, the identification of the collected species using integrative systematics, screening for specific bioactivities for selected industries, identification of the bioactive metabolites and their sustainable production, business plan development, marketing strategy, where legal and ethical aspects to be considered along with adherence to strict guidelines for protection of the environment and sustainability. These pipelines will serve as guidelines and tutorials for future product development and will enable the transfer of knowledge between disciplines. These pipelines will highlight the complementary transdisciplinary aspect of marine biotechnology and as a link with other sectors of biotechnology. According to the principles sustainability the supply chain decision-making will require the inclusion of social and economic aspects together with environmental aspects. Thus, the Action will apply an integrated framework for Life Cycle Sustainability Assessment (LCSA). Wherever possible, it will combine physical LCA considering different environmental impact categories (e.g. climate change, eutrophication or acidification) at different life-cycle levels (partial LCA) with social LCA (SLCA) and Life Cycle Costing (LCC), based on UNEP/SETAC guidelines. The approach used in this Action will build on existing models (Perez-Lopez et al., 2018). It will also follow the methodological framework for conducting LCA as outlined by the International Standards Authority (ISO) 14040 series.

3. **Sharing infrastructure**. There is an increasing need to create a bridge between research and innovation capabilities from the academia and business sectors. This includes the availability of the research infrastructure, thereby providing access to a range of new tools and facilities to allow marine biotechnology to thrive. Many of the tools and techniques used in marine biotechnology are widely used in other areas of science and technology. Engaging in collaborative research projects is one way of providing access to these facilities and encouraging multidisciplinary research. Ocean4Biotech will enable the diverse actors to share their expertise and infrastructure, mostly through short-term scientific missions and new collaborative activities. Preference will be given to users from the less

[7] https://www.eurekalert.org/pub_releases/2018-05/scoe-elt051718.php

research-intensive countries[8] or early career investigators that need access to state-of-the-art analytical equipment, microbial cultures or screening facilities.

4. **Responsible Research and Innovation**. The ocean should be monitored, valorized and governed in a sustainable manner to generate the maximum benefit to science and society but limiting the negative footprints on the marine environment. This will be addressed within the Action by adopting the Responsible Research and Innovation (RRI) concept, which is based on six pillars.

(i) Ethics. We are all responsible for the stability and resilience of the Earth systems (Barbier et al., 2018). Accordingly, ethical issues and challenges will be identified, addressed and used to advocate for protection of marine ecosystems and promote responsible resource management and environmental policies together with societal awareness.

(ii) Open access. To efficiently co-create knowledge and capitalize from previous research, it is vital to consider transparency, efficiency, traceability, access to data, reciprocal relations, biosafety, nature conservation and transfer of knowledge to third countries.

(iii) Gender equality will be promoted throughout the Action by empowering especially early career and female colleagues to apply for managerial roles and in the future establish and lead consortia for valorization of marine biotechnology products.

(iv) Governance. Although the marine biodiversity has no borders, access to natural resources is framed under the Convention of Biological Diversity, promoting the conservation of biodiversity, the sustainable use of biological entities and their fair and equitable sharing. The latter is also covered in the Nagoya Protocol, which provides a legal framework for the fair and equitable sharing of benefits arising from the use of genetic resources which may sometimes delay or block certain research activities.

(v) Public engagement. Action participants will employ communication tools and different activities to further inform legislative authorities, researchers and industry with the aim of facilitating the regulatory requirements that are sometimes a bottleneck to transnational collaboration.

(vi) Science education. We will focus many of our activities into education of the next generation of researchers (i.e. early career investigators), with a special focus on the countries that are less research intensive, i.e. the so-called inclusiveness target countries[9]. These countries have developed their national strategic priorities in the frame of the EU Smart Specialization Strategy (S3), aiming to ensure a balanced development between regions[10]. Since marine biotechnology, including its products and applications, is well represented in all national S3 priorities, the timing is perfect to develop capacity-building educational opportunities that span beyond the traditional academic curricula. We will enable closing the educational gaps in three ways. (i) By short term scientific missions, which are mobility activities that involve a direct hands-on interaction and experience abroad. (ii) By offering financial opportunities for active participation in conferences that target any of the marine biotechnology related topics. (iii) Importantly, our trainings and workshops, that will be publicly promoted, will cover topics that integrate academy, technological centers and industry (as also promoted by the EuroMarine Working Group, 2019). By offering multidisciplinary skills, this

[8] https://www.cost.eu/who-we-are/cost-strategy/excellence-and-inclusiveness/

[9] https://www.cost.eu/who-we-are/cost-strategy/excellence-and-inclusiveness/

[10] https://ec.europa.eu/jrc/en/research-topic/smart-specialisation

strategy will avoid the risk of training a marine-related workforce that the market may not absorb (EuroMarine Working Group, 2019).

5. **Knowledge co-creation and integration**. (i) The Action will be geographically inclusive as it will produce an open-access database of exploitable species for marine biotechnology in the Ocean4Biotech participating countries. In addition to the World Register of Marine Species (WoRMS[11]), this Action participants will focus on those species with putative biotechnological potential. (ii) The Action will be inclusive in the biological sense and include species regardless of the kingdom (from bacteria and algae to zooplankton and other species that are suitable for exploitation). (iii) Methodologically, the participants will integrate all levels of the biotechnological pipeline; from bioprospecting to cultivation, biological screening, compound isolation and optimization of the isolation process, and structure elucidation. (iv) This is a truly transdisciplinary Action, integrating expertise and including experts from various fields: marine (micro)biology, chemistry, food science, agriculture, pharmacology, medicine, environmental protection, engineering, energy, data science, omics techniques, statistics, law, policy making, economy, business planning, and more. The network will transfer knowledge from traditional academic institutions to exploitation industries leading to the elaboration of ecosystem services linked to policy makers' priorities, citizens, industry and SMEs.

Conclusion

This Ocean4Biotech COST Action will contribute to the implementation of the Bioeconomy Strategy and the European Green Deal[12]. It will also mainstream the responsible research and innovation principles among the scientific and industry communities to foster the interaction between marine scientists and other marine biotechnology stakeholders, including the general public. Such interaction will be multidirectional rather than top-down and co-creative instead of just being introduced by the authorities and/or knowledge holders. Outreach and communication activities will provide information to the broad community and improve their capacity to understand the challenges and opportunities to make appropriate decisions in the field of marine biotechnology. An inclusive, integrative approach is essential to catalyze the expansion of marine biotechnology in Europe and worldwide and to finally harvest the products of this promising field of research. Finally, the establishment of interdisciplinary connections and collaborations during Ocean4Biotech's lifetime will not only lead to future research collaborations that include industrial representatives as well, but also provide establishment of communication channels with policymakers, governments, and other stakeholders, including the public. This will eventually enable beneficial social and environmental impacts that will ultimately contribute to a more efficient and sustainable use of marine bioresources.

[11] http://www.marinespecies.org/

[12] https://ec.europa.eu/info/sites/info/files/european-green-deal-communication_en.pdf

Conflict of Interest

Francesco Bertoni: institutional research funds from Acerta, ADC Therapeutics, Bayer AG, Cellestia, CTI Life Sciences, EMD Serono, Helsinn, ImmunoGen, Menarini Ricerche, NEOMED Therapeutics 1, Oncology Therapeutic Development, PIQUR Therapeutics AG; consultancy fee from Helsinn, Menarini; expert statements provided to HTG; travel grants from Amgen, Astra Zeneca, Janssen-Cilag AG, Jazz Pharmaceuticals, PIQUR Therapeutics AG

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

AR designed the article concept and drafted the manuscript. All authors read, commented, improved and approved of the final version of the manuscript.

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Supplementary Materials

Supplementary Table S1: Examples of the past and current international initiatives in the field of marine biotechnology in Europe. The level column represents the targeted involvement within each initiative (industry, research community, legislative authorities, general public, environment protection; they are presented in Figure 2 and in the main text).

Supplementary Table S2: A SWOT analysis used to plan and assess the necessity of establishing marine biotechnology interdisciplinary networks such as COST Action CA18238 (Ocean4Biotech).

Figure legends

Figure 1: Schematic representation of a bioprospecting protocol for the extraction of valuable bioactive compounds from marine organisms (adapted from Galanakis, 2019).

Figure 2: Major prerequisites for the establishment of sustainable actions in marine biotechnology.

Figure 1.TIF

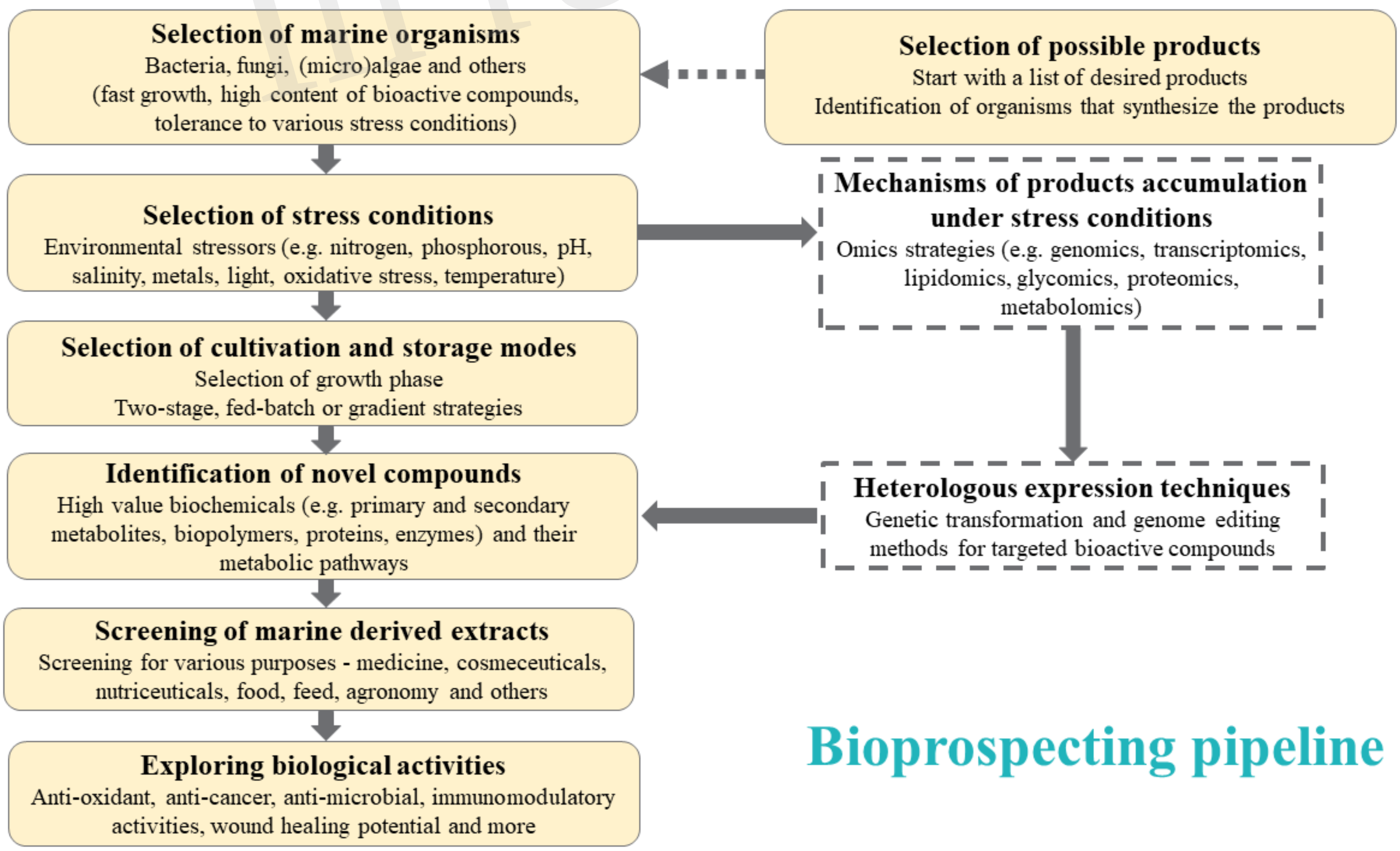
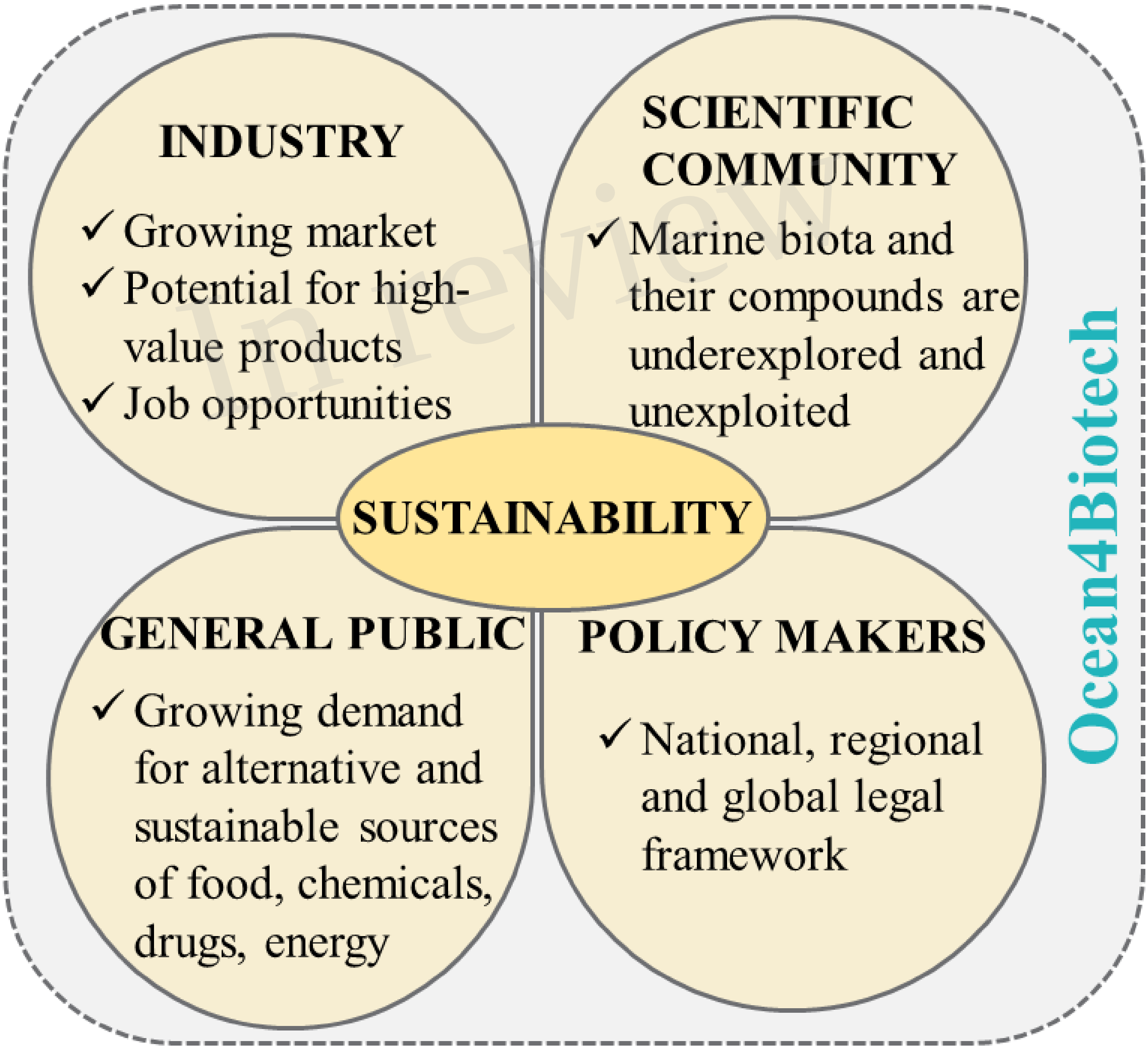

Selection of marine organisms
Bacteria, fungi, (micro)algae and others
(fast growth, high content of bioactive compounds,
tolerance to various stress conditions)
Selection of possible products
Start with a list of desired products
Identification of organisms that synthesize the products
Selection of stress conditions
Environmental stressors (e.g. nitrogen, phosphorous, pH,
salinity, metals, light, oxidative stress, temperature)
Mechanisms of products accumulation
under stress conditions
Omics strategies (e.g. genomics, transcriptomics,
lipidomics, glycomics, proteomics,
metabolomics)
Selection of cultivation and storage modes
Selection of growth phase
Two-stage, fed-batch or gradient strategies
Identification of novel compounds
High value biochemicals (e.g. primary and secondary
metabolites, biopolymers, proteins, enzymes) and their
metabolic pathways
Heterologous expression techniques
Genetic transformation and genome editing
methods for targeted bioactive compounds
Screening of marine derived extracts
Screening for various purposes - medicine, cosmeceuticals,
nutriceuticals, food, feed, agronomy and others
Exploring biological activities
Anti-oxidant, anti-cancer, anti-microbial, immunomodulatory
activities, wound healing potential and more
Bioprospecting pipeline

Figure 2.TIF


INDUSTRY
✓ Growing market
✓ Potential for high-value products
✓ Job opportunities
SCIENTIFIC COMMUNITY
✓ Marine biota and their compounds are underexplored and unexploited
SUSTAINABILITY
GENERAL PUBLIC
✓ Growing demand for alternative and sustainable sources of food, chemicals, drugs, energy
POLICY MAKERS
✓ National, regional and global legal framework
Ocean4Biotech