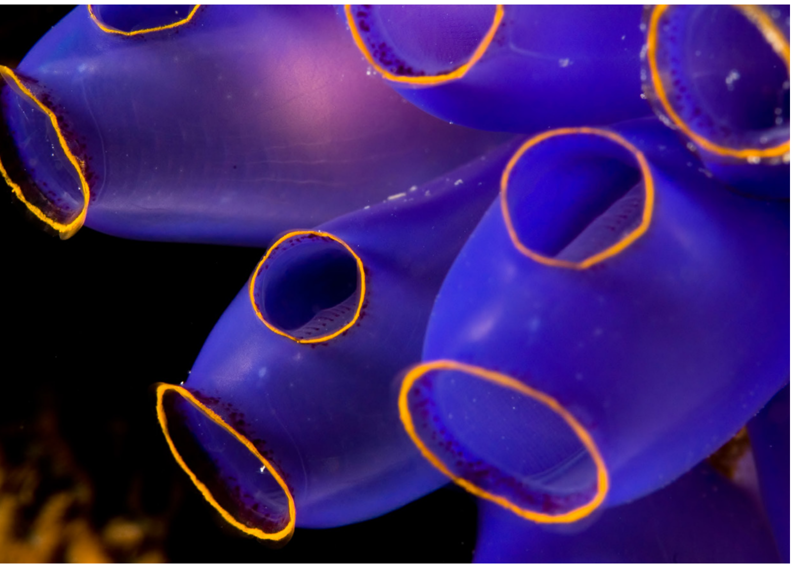
MARINE BIODISCOVERY IN SOUTH AFRICA

Science, conservation, governance and equity

September 2022



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DESIGN

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SUGGESTED CITATION

Lavelle, J. and Wynberg, R. 2022. Marine biodiscovery in South Africa. Science, conservation, governance and equity. One Ocean Hub and University of Cape Town. Pp. 64

ACKNOWLEDGEMENTS

We thank the participants in this research for sharing their insights and experiences. This research is supported by the One Ocean Hub, University of Strathclyde through a partnership with the University of Cape Town, and by the South African Research Chairs Initiative of the Department of Science and Innovation and the National Research Foundation.

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PHOTOGRAPHS

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ACRONYMS

ABS	Access and Benefit Sharing
ACEP	African Coelacanth Ecosystem Project
BABS	Bioprospecting, Access and Benefit Sharing Regulations
BB-BEE	Broad-Based Black Economic Empowerment
BBNJ	Biodiversity of Areas Beyond National Jurisdiction
BSA	Benefit-sharing Agreement
CAMERA	Community Cyberinfrastructure for Advanced Marine Microbial Ecology Researcher and Analysis
CITES	Convention on International Trade in Endangered Species
CBD	Convention on Biological Diversity
DDBJ	DNA Data Bank of Japan
DFFE	Department of Forestry, Fisheries and Environment
DSI[1]	Department of Science and Innovation
DSI	Digital Sequencing Information
EEZ	Exclusive Economic Zone
ENA	European Nucleotide Archive
GBIF	Global Biodiversity Information Facility
ILK	Indigenous and Local Knowledge
IP	Intellectual Property
IPRs	Intellectual Property Rights
IPR-PFRD	Intellectual Property Rights from Publicly Financed Research and Development
JCVI	J. Craig Venter Institute

MTA	Material Transfer Agreement
MAT	Mutually Agreed Terms
MOU	Memorandum of Understanding
NACI	National Advisory Council on Innovation
NCBI	National Center for Biotechnology Information
NCI	National Cancer Institute
NEMA	National Environmental Management Act
NEMBA	National Environmental Management: Biodiversity Act
NIPMO	National Intellectual Property Management Office
NRF	National Research Foundation
NP	Nagoya Protocol
PIC	Prior Informed Consent
R&D	Research and Development
SAIAB	South African Institute for Aquatic Biodiversity
SANBI	South African National Biodiversity Institute
SA-UK AAI	South Africa-UK Antibiotic Accelerator Initiative
TOPS	Threatened or Protected Species
TRIPS	Trade Related Intellectual Property Rights
UNCLOS	United Nations Convention on the Law of the Sea
UK	United Kingdom
US	United States

EXECUTIVE SUMMARY

INTRODUCTION

Marine ecosystems and biodiversity are critical to global food security, planetary health and human wellbeing. The "ocean genome", the genetic material present in all marine biodiversity, including both the physical genes and the information they encode (so-called digital sequence information, or DSI), holds enormous potential for improving the quality of human life and contributing significantly to economies as marine organisms offer unique genetic resources that can be used for a range of applications including pharmaceuticals, nutraceuticals, cosmeceuticals, biofuels and agriculture.

Globally, South Africa has the third highest levels of marine endemism, with an estimated third of its marine biodiversity endemic to the area, owing to its unique biogeography. As a biodiversity hotspot, South Africa's marine environments have long been of interest as a source of novel compounds, with early biodiscovery dating back to the early 1970s. The richness of South Africa's marine biodiversity offers exceptional opportunities for marine biodiscovery and is of worldwide interest for novel compounds.

Today there exists a vibrant research community dedicated to exploring South Africa's marine genetic resources. Significant research capacity exists in-country to carry out all stages of the discovery phase, working actively through local and international partnerships to complement expertise, share resources, develop research capacity and enable opportunities for commercialisation.

Several international governance instruments provide an important platform for the development of these research partnerships and to enable equitable benefit sharing, including conservation of the ocean genome. These include the 1992 Convention on Biological Diversity (CBD), its 2014 Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation, and the United Nations Convention on the Law of the Sea (UNCLOS). The CBD and its Nagoya Protocol require countries who provide genetic resources and associated traditional knowledge, and those who access and develop these resources, to enter into mutually agreed terms based on prior informed consent before access to genetic resources is granted (so-called access and benefit sharing, or ABS). This applies to areas within national jurisdiction, although negotiations are ongoing for so-called "biodiversity beyond national jurisdiction" (BBNJ) under the UN Convention on the Law of the Sea.

As a signatory to these agreements, South Africa has developed a suite of laws and policies to protect the marine environment and innovations derived from marine genetic resources, as well as associated traditional knowledge. These are implemented by the Department of Forestry, Fisheries and Environment (DFFE) and the Department of Science and Innovation (DSI[1]).

This report is one component of broader global research being undertaken through the One Ocean Hub initiative to understand challenges relating to the equitable use and sustainable governance of marine genetic resources. It aims to provide an in-depth review of marine biodiscovery in South Africa, detailing historical and current activities, the governance framework, and existing (dis)connections in science and policy. The intention is for this understanding to be used to explore opportunities for harmonising science and policy to enable more equitable, effective, sustainable and coherent approaches for the governance of marine biodiscovery in South Africa.

The report is supported by data from interviews with 18 individuals from government and research institutions including scientists, policymakers, regulators, NGOs and legal experts. In addition, literature and other secondary sources, including partnership agreements and permits were reviewed.

KEY COMPONENTS OF THE REPORT

- Provides an overview of the research activities and expertise of the marine biodiscovery community in South Africa;
- Identifies research capacity constraints and associated opportunities for benefit sharing;
- Explores how broader societal and conservation objectives can be supported by marine biodiscovery;
- Describes the link between Indigenous and local knowledge (ILK) and marine biodiscovery;
- Untangles the regulatory and institutional framework as it applies to marine biodiscovery;
- Illuminates current scientific practice relating to laws and policies regulating access and benefit sharing from marine genetic resources;
- Identifies legal and policy gaps and challenges to effective regulation.

KEY FINDINGS

South Africa as a scientific hub for marine biodiscovery

- The richness of South Africa's marine biodiversity offers **exceptional opportunities for marine biodiscovery** and is of worldwide interest for novel compounds.
- There is a **strong biodiscovery research community** in South Africa working actively through local and international partnerships to complement expertise, share resources, develop research capacity and enable opportunities for commercialisation.
- Significant research capacity exists in-country to carry out all stages of the discovery phase but South Africa faces **funding, resource and infrastructure constraints for commercialisation**.
- The expense and difficulty of obtaining biological samples and the limited supply of natural products from these samples, combined with significant advances in science and technology, has led to a surge in the use of "omics" technologies to elucidate the genes and pathways responsible for producing bioactive compounds. The result is a **mass of DSI that is increasingly difficult to trace** from origin to end-product, particularly in the commercialisation phase.
- A key challenge for South Africa is to leverage international **support for expensive deep-sea research.**

Equitable research partnerships and benefit sharing

- There has yet to be a successful commercial product arising from the use of South African marine genetic resources, although several candidate species have shown potential. Benefit sharing for biodiscovery in South Africa has thus largely centred on the development of **scientific research partnerships**. This has yielded important benefits for the South African research community, including the training of postgraduate students, access to external repositories, the development of local repositories, joint publications, knowledge sharing, technology transfer, long-term strategic international research collaborations and developing critical mass in fields such as microbiology.
- In earlier years, partnerships often focused on capacity development through staff and student knowledge exchange and training. While opportunities for expanding research capacity continue to be important, this focus has changed towards **partnerships with specialised expertise and infrastructure** required for the whole pipeline that is not yet available in South Africa. These partnerships result in long term collaborations that span decades and enable support for the development of research capacity, facilitate funding, spark innovation and strengthen transparency and reciprocity in the scientific community.
- Samples are often exchanged within local research partnerships through Material Transfer Agreements (MTAs) that detail what research will be undertaken. Within international research partnerships, **biological samples are not readily exported** due to concerns related to third party use and traceability.
- The **link between marine biodiscovery and Indigenous and local knowledge (ILK)[1] is currently unclear**. Unlike terrestrial biodiscovery, marine biodiscovery in South Africa has not yet or knowingly made direct use of ILK. However, there is recognition of the use of marine resources by local communities for traditional medicine and it is possible that ILK has been used in biotrade products such as kelp. Should the need for a benefit-sharing agreement arise, such links will need to be considered together with the role of coastal communities as custodians of marine genetic resources.

[1] For the purpose of this report the terms "traditional knowledge" and "indigenous knowledge" are used interchangeably. "Traditional knowledge" is a term used in the CBD and other international agreements, as well as in South Africa's NEMBA and the BABS Regulations. "Indigenous knowledge" is used in South Africa's Indigenous Knowledge Systems Act.

Traceability and data sharing

- Biological samples are not readily exported outside of South Africa, however, **data are increasingly shared** within international partnerships.
- Good practices within the scientific community are increasingly ensuring **data traceability back to the sites of collection**, with local identifiers used by researchers for materials and data derived from resources for biodiscovery. Data are typically maintained in different, locally-based databases linked to particular institutions or projects. Such information may include the location of sample collection, taxonomic identification, links to DNA sequences, biological assay data and biochemical compounds obtained. This level of traceability is not required by law but enables researchers to accurately identify materials of interest for further investigation.
- Researchers are often **cautious about sharing genetic sequence data on public databases** in the absence of patent protection and a mechanism to ensure benefit sharing from use of this DSI.

Biodiversity conservation benefits

- **Benefits from marine biodiscovery can contribute to conservation** through the development of repositories and databases, supporting taxonomic and other fundamental biodiversity research, and training, capacity building and technology transfer to undertake biodiversity-based research. However, these have not been significant to date.
- Due to technological advances, **marine biodiscovery poses less of a biodiversity threat** to species than it did historically, with other environmental stressors and economic activities such as mining, fishing and pollution playing a much bigger role in biodiversity loss.
- **Partnerships** between government agencies such as the South African National Biodiversity Institute (SANBI) and research institutions offer an opportunity for conservation benefits to be enhanced. Similarly, conservation measures can be incorporated into benefit-sharing agreements, including research funding for boats and equipment, and resources for sampling expeditions to generate inventories of taxonomic and distribution data important for monitoring and marine spatial planning.
- **Communicating the benefits of marine biodiscovery** is an important strategy to motivate for the establishment of marine protected areas, marine spatial planning and a more holistic approach to the ocean economy.

The governance of marine biodiscovery

- South Africa has a **strong access and benefit sharing regulatory framework** in place to protect indigenous biological resources and realise benefits from its research and commercialisation. However, permitting processes for biodiscovery across multiple institutions and at national and provincial levels can hinder research programmes.
- At times, the **stringency of the regulations has led to delays in research programmes** and hesitancy by the international scientific community to collaborate with South African researchers.
- There is a **grey area in permitting procedures** between research that is conducted purely for scientific purposes to generate knowledge and research done for commercialisation as the end goal. This also reflects the challenges of separating out research and commercialisation in the R&D process.
- The ABS legal framework in South Africa was designed with a focus on terrestrial plants and as such challenges have arisen in the application of the framework to marine biodiscovery. An increasing focus on microorganisms and DSI adds to the fact that the **ABS regulatory**

framework is not always fit for purpose.

- This is further complicated by the **range of environments** from which samples can be collected which do not always have clear cut regulations or institutions.
- South Africa's ABS legal framework regulates current biodiscovery. **Pre-existing *ex-situ* collections based on historical material fall outside of the regulatory framework** and there is a lack of clarity about how these should be managed and regulated.

Alignment with national imperatives

- The South African government's **Phakisa Programme**, a fast results delivery initiative aimed at boosting economic growth and job creation, includes projects on both the Oceans Economy and the Biodiversity Economy yet **does not include an explicit focus on marine genetic resources and biodiscovery**. This is likely because (a) its social benefits are less obvious than those arising from terrestrial biodiversity, (b) the resources it often targets are, in the case of microbes, "invisible" and out of the public and regulatory view, (c) for biotrade, are largely within the realm of fisheries management, and (d) for biodiscovery, have not yet seen commercial success.
- **Benefits from marine biodiscovery can contribute to society** through funding for research on neglected and locally relevant pathogens as well as other research areas that are tailored towards environmental and social priorities in South Africa. Opportunities thus exist for government to engage a range of societal actors including academia, citizens, industry and others in research and innovation to better align biodiscovery and its outcomes with the values, needs and expectations of society.

KEY RECOMMENDATIONS

- The key to successful benefit sharing is a **light-touch governance approach** that promotes marine biodiscovery and international collaboration through streamlined permitting processes that are aligned with scientific best-practice in data management and traceability.
- **Permitting processes require clarification and streamlining across agencies** with a focus on the provision of clear institutional guidelines from each agency specific to marine biodiscovery. These guidelines should be readily available online in a "one-stop-shop" with links to the relevant forms and submission contact details.
- **Attention needs to be given by regulators to the way in which permitting occurs for microorganisms and for different kinds of marine environments and ecosystems.**
- **A policy for the way in which DSI is regulated and managed should be developed**, and linked to a broader policy for DSI, ABS and scientific research in South Africa.
- **A national marine biodiscovery analysis** should be initiated to identify the strengths and gaps towards a strategy for developing South Africa's capability for commercialisation.
- **Local and international partnerships are crucial to the biodiscovery pipeline**. Governance approaches should support the facilitation of these partnerships to promote marine scientific research.
- **Resources should be directed towards gaps in the biodiscovery pipeline**, most notably chemical analysis, upscaling production of bioactive compounds and pre-clinical development of products.
- To prevent overlap and use resources more efficiently, **efforts should be made to enhance collaboration between scientists and the coordination of projects**.
- **Benefit-sharing agreements and partnerships should be leveraged** to support the development of national biobanks and databases, fundamental biodiversity research, and training, capacity building and technology transfer for marine biodiscovery.
- **Steps should be taken by regulators and researchers to ensure that marine biodiversity conservation and sustainable use is explicitly supported** in the development of biodiscovery research agreements, partnerships and commercialisation arrangements.
- **Priority should be given to supporting research that targets local environmental and social needs.**

1. INTRODUCTION

Marine ecosystems and biodiversity are critical to global food security, planetary health and human wellbeing. The "ocean genome", the genetic material present in all marine biodiversity, including both the physical genes and the information they encode, holds enormous potential for improving the quality of human life and contributing significantly to economies. This is because marine organisms offer unique genetic resources that can be used for a range of applications including pharmaceuticals, nutraceuticals, cosmeceuticals, biofuels and agriculture (Blasiak *et al.* 2020a).

While local communities have long used ocean resources for food, medicine and livelihoods, it was only from the 1960s that scientists began to probe systematically the oceans for useful therapeutics (Jaspers *et al.* 2016). Biodiscovery is defined as the targeted search for and development of new sources of chemical compounds, genes, microorganisms, macroorganisms, and other valuable products from nature. Marine organisms are of great interest to researchers working on biodiscovery as they often have highly developed defence systems to survive in hostile conditions such as extreme temperatures, varied pressures and lack of sunlight. This is reflected by the myriad of secondary metabolites (or natural products) that they produce to defend themselves against predators and in response to inter-species competition for limited resources. Many of these compounds have no terrestrial analogues and are unique in terms of chemical structure and biological activity (Jaspers *et al.* 2016). As such, the pharmaceutical sector is active in seeking novel drugs from marine organisms to find solutions to antibiotic resistance, cancer and other incurable diseases, and to meet the increase in demand for bio-based drugs. Marine organisms also hold information for understanding various fundamental phenomenon of life not yet understood (Bhatia and Chugh 2015).

South Africa is increasingly turning to the ocean in recognition of the rich marine resources and the inherent economic potential it offers. Owing to the country's high levels of endemism there has long been interest in South Africa's marine environments as a source of novel compounds with early biodiscovery dating back to the early 1970s. Research interest in the region's marine resources continues to grow and several international research collaborations for marine drug discovery are underway. This report examines the marine biodiscovery seascape in South Africa including historical and current activities, the governance framework and its impact on research and innovation, research partnerships within and across borders, benefit sharing and the link between marine biodiscovery, Indigenous and local knowledge and biodiversity conservation. The purpose of the report is to provide policymakers, regulators and scientists with a comprehensive review of marine biodiscovery in South Africa to:

i) identify constraints in the biodiscovery pipeline towards a national strategy;
ii) identify any existing disconnections in law, science and policy that require attention;
iii) identify opportunities for biodiscovery to contribute to conservation and sustainable use of marine biodiversity;
iv) contribute to the development of a policy for DSI, ABS and scientific research in South Africa;
v) contribute to international processes related to governance of marine genetic resources.

The research is part of the One Ocean Hub, an international programme of research for sustainable development funded by UK Research and Innovation (UKRI) through the Global Challenges Research Fund (GCRF). The One Ocean Hub seeks to bridge current disconnections in law, science and policy and integrate governance frameworks to balance multiple ocean uses with conservation.

2. GLOBAL SCIENCE AND GOVERNANCE CONTEXT

2.1 GLOBAL TRENDS IN MARINE BIODISCOVERY

The targeted search for compounds with biological activity against human diseases began in the late 1960s, but structures of compounds with high potency and selectivity were not defined until the 1980s. Extensive funding by the United States' (US) National Cancer Institute along with its commitment to collect marine genetic resources globally meant that the focus was on the treatment of cancer, using compounds mostly collected from shallow tropical reefs and derived from marine invertebrates (Thornburg *et al.* 2018). As a result, five out of the eight clinically approved drugs derived from marine organisms are treatments for cancer; the remaining three are treatments for neuropathic pain, *Herpes simplex* virus and hypertriglyceridemia. Out of these, seven are derived from marine invertebrates and one is derived from an oily fish (Blasiak *et al.* 2020a). There are also 28 natural products in Phase I to Phase III clinical trials with a further 250 in preclinical investigation (MarineLit 2020). Of those in clinical trials, 23 are anticancer agents, two for schizophrenia and Alzheimer's, and one for chronic pain (Jaspers *et al.* 2016). The natural products include compounds derived from sponges, tunicates, cone snails, actinomycetes, nemertine worms, actinobacteria and fungi, amongst others.

In total, close to 33,000 molecular entities have been discovered, with biological activities attributed to these compounds (MarinLit 2020). However, very few have been marketed or are under development. Several reasons account for the slow commercialisation of compounds, including the time and cost it takes to reach the market, difficulties in harvesting the organism, limited samples of natural product in producing organisms, difficulties in isolation and purification procedures, problems in obtaining a sustainable supply of the compound, high toxicity of the active compound, ecological impacts on natural populations, and insufficient investment by pharmaceutical companies (Torjesen 2015).

To address the challenges of obtaining sufficient supply of marine invertebrate-derived natural products, researchers have increasingly turned their attention to investigating marine microorganisms as sources of bioactive compounds. Advances in genomic technologies and bioinformatics allow for the rapid sequencing of genomes and the identification of secondary metabolite gene clusters to predict whether microorganisms under investigation are genetically able to produce chemicals. However, most microbial compounds are still at preclinical stages of development, with only a few in human clinical trials (Mayer *et al.* 2017).

Genomic technologies used to study genes and their functions generate an unprecedented amount of so-called digital sequence information (DSI)[2], making this an intensely data-rich field. As a result, bioinformatics – the collection, classification, storage and analysis of

[2] Digital Sequence Information (DSI) is not a term typically used by the scientific community but has become adopted as a placeholder for negotiations. Terms more commonly employed include genetic sequence data, nucleotide sequence data, nucleotide sequence information, and genetic sequences. Differences in terminology in scientific circles reflect differences in the material referred to, as well as the speed and transformative nature of technological change today, which make it difficult to harmonise terminology (Laird and Wynberg 2018). In ABS policy discussions, differences in terminology often reflect divergent views of what falls within the scope of the Nagoya Protocol and national laws, ranging from the inclusion of DNA and RNA sequences, through to protein sequences and their resulting metabolites (AHTEG 2020).

complex biological data – has grown alongside genomic technologies in order to store, retrieve, and analyse these vast and growing amounts of information. Advances in sequencing and bioinformatics have in turn given rise to metagenomics, also known as environmental genomics, in which researchers sequence and analyse genetic material found in environmental samples, usually from soil or water (Laird and Wynberg 2018). Advances in chemoinformatics, such as Global Natural Products Social Molecular Networking, allow scientists to verify the latent capacity of microorganisms to produce compounds, massively speeding up the biodiscovery process (Blasiak *et al.* 2020a). Advances in assay technology enable the use of less material in bioassays while obtaining better quality data with higher information content and there have also been improvements in compound isolation and structure determination. To bypass chemical synthesis of bioactive compounds, research has also focused on determining biosynthetic and chemoenzymatic pathways for synthesis of compounds, manufacture of molecular processes, and modification or even perhaps creation of organisms (Glaser and Mayer 2009).

The development of anticancer drugs is the main focus of big pharma and a promising area in cancer research is around antibody drug conjugates whereby toxic natural products are linked to an antibody that delivers the toxic drug specifically to the cancer so as not to affect normal cells. The enzymatic processes of the cancer cell, dubbed "the warhead", free the toxic natural product from the antibody in the cancer cells and provide targeted treatment (Newman 2019). However, alongside anticancer drugs, the need for antivirals is of global concern with clinically approved antiviral drugs currently available for only 10 of the more than 220 viruses known to infect humans, 80% of which are naturally persistent in animals. Viruses, and in particular, RNA viruses, dominate the World Health Organisation's current list of ten global health threats yet vaccines exist only for 14 human viruses (mostly for influenza) (Adamson *et al.* 2021).

New antibiotics are also urgently needed, particularly to tackle the increase in antibiotic-resistant bacteria. According to the World Health Organisation, antibiotic resistance is currently one of the biggest threats to global health, food security, and development yet new antibiotic development has moved slowly as there is diminished pharmaceutical investment (Fair and Tor 2014; Outterson *et al.* 2015). There are few compounds in the antibiotic development pipeline with approximately 23 antibacterial compounds in preclinical pharmacological research (Mayer *et al.* 2013). The slow activity is partly historical as following the discovery of penicillin, there was a surge in antibiotic discovery in the 1950s and 1960s but pharmaceutical companies subsequently lost interest, believing that the problem of bacterial pathogens had been solved. It is also attributed to an unattractive risk-reward ratio for pharmaceutical companies and as of 2013 there are only four multinational pharmaceutical companies with antibiotics divisions left (Boucher *et al.* 2013). Antibiotic courses are typically administered for very short durations making them far less profitable than drugs used to treat chronic ailments, new antibiotics are typically held in reserve and only prescribed for infections that more established antibiotics can't treat and regulatory hurdles have also diminished the interest of major pharmaceutical companies as the tolerance of adverse side effects has recently been decreased for many drug classes (Fair and Tor 2014; Outterson *et al.* 2015). Antibiotics developed from actinobacteria, which occur in almost any kind of environment, account for 70-80% of all antibiotics currently on the market. The importance of actinobacteria, in particular *Actinomycetes*, is due to their ability to produce different classes of antibiotics in terms of chemical structure and mechanisms of action and they are a prime resource for the discovery of new natural products as they have unique enzymatic sets that generate compounds potentially useful for diverse purposes (De Simeis and Serra 2021).

Another key challenge in marine biodiscovery is the equitable development of drugs, as pharmaceutical companies focus on diseases prevalent in wealthier countries and have limited appetite to develop drugs for orphan diseases and neglected pathogens unless they become a threat to wealthier countries. For example, the US Food and Drug Administration approved the first Ebola virus vaccine only in December 2019 to suppress an outbreak in the Democratic Republic of Congo, despite vaccine trials being initiated in primates as early as 2000 (Adamson *et al.* 2021).

Alongside development of natural products for high-value pharmaceuticals are the nutraceutical and cosmeceutical industries. These medium-value products are faster to develop for markets and many companies choose to follow the functional product route as it offers lower risk and a quicker potential return on investment than the high risk-reward pharmaceutical market. Marine resources have huge nutraceutical potential (Hill and Fenical 2010; Suleria *et al.* 2015) and products include omega-3 fish/algal oil, phospholipids (bound omega 3-fatty acids), micro/macro algal nutrition supplements, fish proteins and peptides, hydrolysates, shellfish chitin, fish collagen and mineral supplements (Jaspers *et al.* 2016). Commercialised marine cosmeceuticals include Estée Lauder's Resilience line with pseudopterosins derived from the Caribbean gorgonian (seawhip) *Pseudopterogorgia elisabethae* and cosmeceuticals derived from vent bacteria namely, Abyssine 657 (Meyer/L'Oreal) and Venuceane (Sederma/Croda) (Blasiak *et al.* 2020a). Marine biodiscovery also holds potential for the production of bulk chemicals, enzymes for industrial processes and laundry detergents, probiotics in animal feed, and packaging alternatives to plastic.

2.2 GOVERNANCE OF MARINE BIODISCOVERY

As awareness of the value of the ocean genome has grown, so too has the complexity of the international and national legal, institutional and ethical contexts that govern it (Blasiak *et al.* 2020a, b). Genetic sequence data and innovations based on such digital information are now the subject of patent and ownership claims raising international debates on the ethical considerations of access and benefit sharing from marine genetic resources.

The 1982 United Nations Convention on the Law of the Sea (UNCLOS) contains provisions for governing, *inter alia*, limits of national jurisdiction over ocean space, access to seas, navigation, protection and preservation of the marine environment, exploitation of living and non-living resources, scientific research, seabed mining and the settlement of any disputes concerning application and interpretation of the Convention. The Convention represents a codification of international law rules for states to observe in marine-related operations and recognises the sovereign rights of states over their marine biodiversity. More recently, a series of intergovernmental conferences have been held to negotiate the terms of an international legally binding instrument under UNCLOS on the conservation and sustainable use of marine biodiversity of areas beyond national jurisdiction (BBNJ). The instrument is focused on four main elements: 1) marine genetic resources, including questions on the sharing of benefits; 2) area-based management tools, including marine protected areas; 3) environmental impact assessments; and 4) capacity building and the transfer of marine technology. The fifth session of the negotiations was held in August 2022 but no agreement was reached. Negotiations have been suspended until early 2023. While potential approaches have been suggested, negotiating states have not yet agreed how to implement access and benefit sharing (ABS) of marine genetic resources in the unique geopolitical conditions of the areas beyond national jurisdiction (Humphries *et al.* 2020; Laird *et al.* 2020; Humphries *et al.* 2021).

Within areas of national jurisdiction, marine resources and associated Indigenous and local knowledge (ILK) have been subject to instances of biopiracy where access to marine genetic resources has been without the knowledge or consent of the state or of local communities and their exclusion from fair and equitable sharing of the benefits arising from the commercialisation of their knowledge (Bhatia and Chugh 2015). The 1992 Convention on Biological Diversity (CBD) and 2014 Nagoya Protocol (NP) on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation have sought to address these challenges and have the objectives of conservation, sustainable use, and fair and equitable benefit sharing. With these agreements in place many of the biodiversity and associated ILK rich countries have introduced policy and legislation for ABS.

However, while access to genetic resources is typically negotiated bilaterally at a national level in accordance with the NP and national ABS policies, the advent of genomics has created a grey and contested space of regulation. Research practices and concepts of ethics and benefit sharing associated with DSI that have evolved in recent decades within the scientific community emphasise openness, transparency, networks and free exchange with genomics data stored in free public databases such as GenBank, ENA (European Nucleotide Archive) and DDBJ (DNA Data Bank of Japan). This has changed the way many researchers work, making possible dynamic knowledge hubs and diffuse scientific collaborations that take place in an increasingly globalised research context. Diverse networks of researchers from industry, government, academia, and community laboratories commonly span the globe in a system of "open innovation" in which users add incremental value through data and knowledge sharing along a chain that involves multiple databases and gene sequences (Laird and Wynberg 2018). By contrast, ABS is a bilateral transactional mechanism that emphasises contracts to define terms of access to genetic resources so that their use can be exchanged for benefits between identified users and providers of these resources (Blasiak *et al.* 2020b). The question of how to regulate DSI under the current protocol remains contested with some parties and stakeholders advocating for its inclusion while others call for a need to delink access from benefit sharing for DSI (Laird *et al.* 2020). A shift in the mechanism from a bilateral approach to a global multilateral benefit sharing mechanism has also been suggested as per Article 10 of the NP and is receiving wide support (Scholz *et al.* 2022).

Another significant problem in current international agreements is the disjuncture between the NP, which recognises the sovereign rights of states (and local communities) over their biological diversity and ILK, and the World Trade Organisation Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPs), which confers monopoly rights through intellectual property rights (IPRs). Under the NP users are required to have Prior Informed Consent (PIC), Material Transfer Agreements (MTA) and Mutually Agreed Terms (MAT) outlining benefit sharing from the use of genetic resources and/or associated traditional knowledge. The TRIPS agreement, in contrast, does not require disclosure of PIC and the country of origin of source material in patent applications. Streamlined multilateral systems for all genetic resources might avoid costly, duplicative, and ineffective tracking systems and could be linked to intellectual property tools to identify phases of commercial utilisation that trigger benefit sharing obligations (Laird *et al.* 2020).

Regulating the sustainable and equitable use of the ocean's biodiversity, genome and resulting innovations is mired in complexity and challenged by the vastness of the ocean's extent, the rapid speed of technological advances and discrepancies between the technologically-rich Global North and biodiversity-rich Global South. Therefore, efforts should be focused on promoting more inclusive innovation and greater equity in marine biodiscovery and broader public and social benefits from the outcomes of research and innovation.

3. SOUTH AFRICA

3.1 OVERVIEW OF BIOGEOGRAPHY

Continental South Africa has a coastline of some 3,650 km and an Exclusive Economic Zone (EEZ) of just over 1 million km^2. The continental shelf is narrow along the east coast (Indian Ocean), but much wider to the west (Atlantic ocean) and especially to the south, where it extends into the large, shallow Agulhas Bank. Waters in the EEZ extend to a depth of 5,700 m and only 25% of the seafloor lies in depths shallower than 1,000 m. Ten percent of the seafloor is between 1,000 and 2,000 m while depths greater than 2,000 m make up 65% of the EEZ (Griffiths *et al.* 2010) (Figure 1).

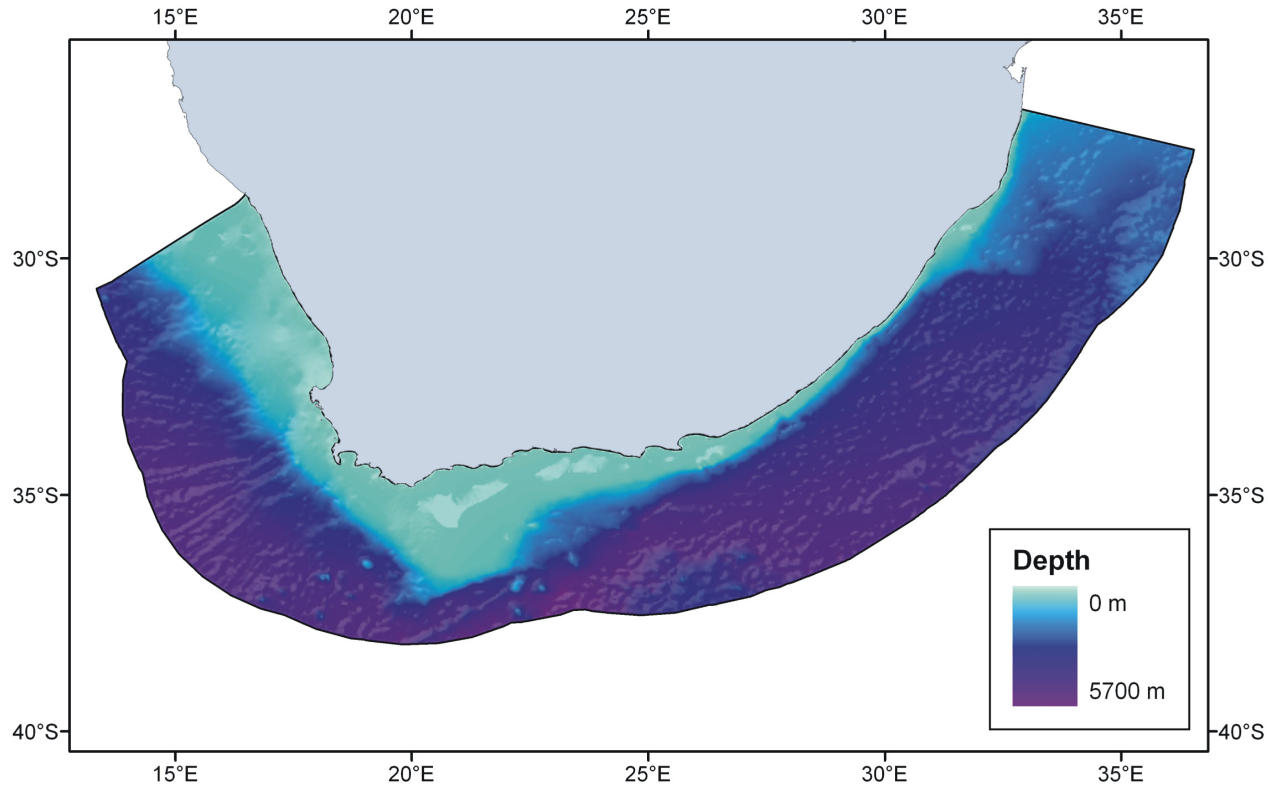

Figure 1: Map showing seafloor depths and the boundaries of South Africa's continental Exclusive Economic Zone (EEZ) (Source: Griffiths *et al.* 2010).

Environmental conditions change considerably from west to east. Studies analysing marine biogeography around the South African coast recognise between two and five broad coastal biogeographic provinces (Stephenson 1939, 1944, 1948; Stephenson and Stephenson 1972; Brown and Jarman 1978; Bustamante and Branch 1996; Turpie *et al.* 2000). The 2004 national assessment of marine biodiversity in South Africa synthesised all existing information and with expert input defined nine marine bioregions, which incorporate both coastal and offshore zones, as shown in Figure 2, with an additional bioregion around the subantarctic Prince Edward Islands. While the coastal bioregions have been well defined by means of detailed faunal and floral analyses, the offshore regions are defined largely by physical criteria (e.g., temperature, depth, substratum).

The cool-temperate Namaqua Bioregion of the west coast and warm-temperate Agulhas Bioregion of the south coast are separated by a broad overlap zone, termed the South-Western Cape Bioregion. On the east coast the subtropical Natal Bioregion, merges in the far north of the country into the tropical Delagoa Bioregion, which extends northward into Mozambique. The Atlantic Offshore Bioregion extends from Namibia to Cape Agulhas, while the West Indian Offshore Bioregion includes the continental slopes of the south and east coasts, meeting the tropical South-west Indian Offshore Bioregion in northern KwaZulu-Natal. A deep-water Indio-Pacific Offshore Bioregion includes the large area off the entire east coast. Within each of these bioregions there exists a variety of localised habitats (e.g., reef, sand, mud) with unique environmental factors and each with their own distinctive biota (Lombard 2004; Griffiths *et al.* 2010).

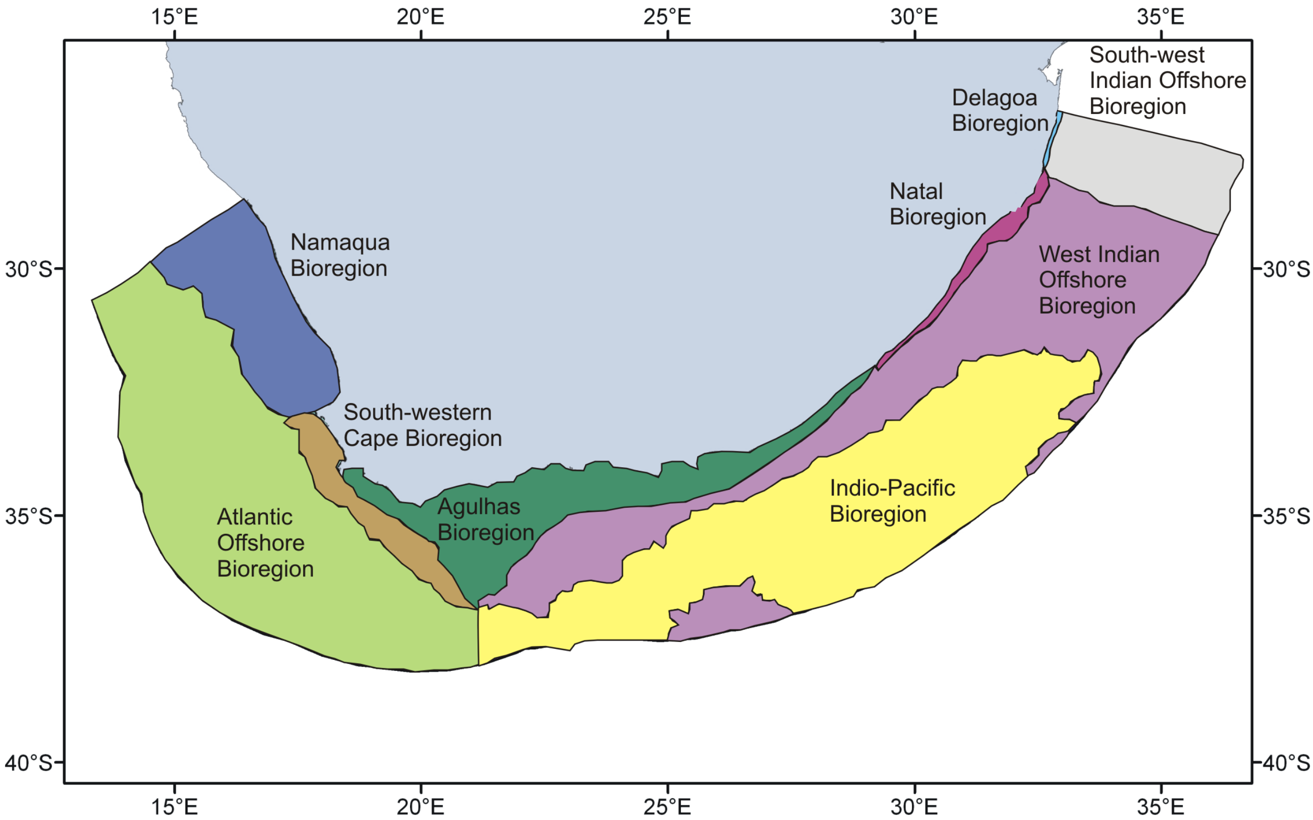

Figure 2: South Africa's nine marine bioregions (Source: Griffiths *et al.* 2010)

The marine environment includes the Atlantic, Indian and Southern Oceans with the contrasting cold Benguela upwelling region and the warm, fast-flowing Agulhas current interacting with the diverse geological setting and topography to drive exceptional marine biodiversity. The broad range of climatic, oceanographic and geological settings results in a wide array of ecoregions and 150 different marine ecosystem types (Skowno *et al.* 2019). While the off-shore colder waters of the west coast support a larger biomass of marine organisms arising from the upwelling of cold nutrient rich water associated with the Benguela current, there is high marine endemism in the Warm Temperate Agulhas ecoregion on the south coast, which is geographically very isolated from other Warm Temperate regions. Globally, South Africa is reported to have the third highest marine endemism with an estimated 33% of its marine fauna found only in its waters (Skowno *et al.* 2019). High levels of endemism in chemically defended species are of obvious interest to those working in marine biodiscovery because of the increased potential for the discovery of novel biologically active chemical entities from these species (Davies-Coleman and Sunassee 2012).

The currently recorded marine biota of South Africa numbers at least 12,914 species, although many taxa, particularly those of small body size, remain poorly documented (Skowno *et al.* 2019). According to Griffiths *et al.* (2010) the coastal zone is relatively well sampled with some 2,500 samples of benthic invertebrate communities that have been taken by grab, dredge, or trawl. However, over 99% of existing samples are from depths shallower than 1,000 m, with 83% from less than 100 m.

3.2 HISTORICAL BIODISCOVERY ACTIVITIES

3.2.1 Pre-1990

The first marine biodiscovery explorations along the South African coast occurred off the Southern Cape and Sodwana Bay (1972-1981) and were facilitated by Professor G. R. Pettit from Arizona State University. These explorations resulted in the discovery of cephalostatin 1, a secondary metabolite from *Cephalodiscus gilchristi* (Figure 3), which was isolated in 1974 and has been shown to bring about apoptosis or controlled cell death in leukemia cancer cells (Pettit *et al.* 1988). Forty-one years later, the isolation and structure of cephalostatin 20 was accomplished by Pettit *et al.* (2015). Cephalostatin 1 together with its 19 closely related naturally occurring analogues are widely regarded as some of the most cytotoxic secondary metabolites ever researched by the NCI (Davies-Coleman and Sunassee 2012).

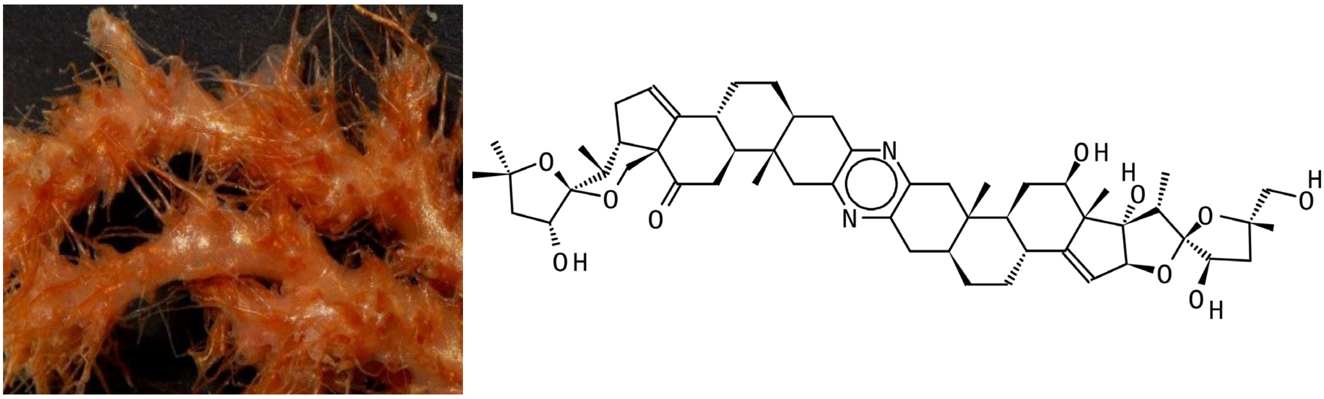

Figure 3: *Cephalodiscus gilchristi* (left) and chemical structure of cephalostatin 1 (Source: commons.wikimedia.org image by Oiseau Furtif)

Initially it was challenging to elucidate the chemical structures of the cephalostatin metabolites present in the *C. gilchristi* extracts, with the structure of cephalostatin 2 only emerging in the literature 13 years later. Cephalostatin 2 is the most consistently cytotoxic compound to cancer cell lines, however the mechanisms by which cephalostatin 2 may be selectively cytotoxic are unknown and the clinical development of cephalostatin 2 has been hampered by problems of supply. Following the initial collection of 166 kg of *C. gilchristi* in 1981, a recollection of 450 kg took place in 1990 and afforded only 100 mg of cephalostatin 2, far short of the multi-gram quantities required for clinical development. Laboratory synthesis is thus the only viable alternative to resolve the supply problem. The successful synthesis of this compound has still not been achieved but remains of great interest for anticancer drug development (Davies-Coleman and Sunassee 2012).

The daunting synthetic challenges of cephalostatin molecular architecture continue to inspire the synthesis of simpler analogues with similar bioactivities to cephalostatin 1 (Davies-Coleman and Veale 2015). Further investigation of the mode of action of cephalostatin 2 may lead to future important advances in cancer chemotherapeutics. While *C. gilchristi* is no longer being collected *in-situ* its limited abundance today is of interest to biodiversity conservationists who recently were only able to find a single specimen on a sampling survey, an outcome perhaps of the two earlier collections.

Other notable African discoveries from the early explorations by Pettit include the spongistatins 4-9 from the orange wall sponge *Spirastrella spinispirulifera* (also *Trachycladus spinispirulifer*) and hallistatin 1 and 2 from the elephant ear sponge *Phakellia carteri* (also *Stylissa carteri*) (Figure 4). While both species occur off the coast of South Africa these discoveries were likely from samples from the Republic of Maldives and the Union of the Comoros.


Figure 4: Orange wall sponge (*Spirastrella spinispirulifera*) (Source: en.wikipedia.org photo by Peter Southwood) and elephant ear sponge (*Phakellia carteri*) (Source: en.wikipedia.org photo by Alexander Vasenin)

3.2.2 1990 – 2012

Following the early biodiscovery research, interest waned until the 1990s when several collaborative marine biodiscovery programmes were initiated. Marine invertebrate biodiscovery expeditions, coordinated from Rhodes University in partnership with the University of the Western Cape and the Department of Environmental Affairs (1990–2004), revealed for the first time the significant latrunculid sponge diversity off South Africa. The continual discovery of new latrunculid species and genera from these expeditions fuelled increasing interest in these sponges and ultimately led to a taxonomic revision of the family Latrunculiidae in parallel with the natural products chemistry and bioactivity studies of the isolated natural products (Hooper *et al.* 1996; Beukes 2000; Samaai and Kelly 2002; Samaai *et al.* 2003; Antunes *et al.* 2004, 2005).

A large cohort of metabolites was isolated from five latrunculid sponge species (*Cyclacanthia bellae, Strongylodesma algoaensis, S. aliwaliensis, Tsitsikamma favus and T. pedunculata*) with the tsitsikammamines from the endemic *T. favus* (Figure 5) within the Agulhas ecoregion showing the most potential for cancer cell cytotoxicity. Tsitsikammamine A has subsequently been successfully synthesised together with a series of 43 analogues and tsitsikammamine C has shown antimalarial activity. While the tsitsikammamines were once thought to be unique to *T. favus* they have since been reported from Australian and Antarctic latrunculid species. Nonetheless, this research has positioned South Africa as a global hotspot of latrunculid sponge biodiversity and the search for new latrunculid sponge species continues (Davies-Coleman *et al.* 2019). Additional species more recently discovered include *Tsitsikamma michaeli*, collected from Algoa Bay, and *Tsitsikamma nguni* from the Garden Route National Park, Tsitsikamma Marine Protected Area (Parker-Nance *et al.* 2019). Molecular networking of the *Tsitsikamma* species has recently revealed makaluvamines for the first time and the existence of two distinct *T. favus* chemotypes, the one producing predominantly discorhabdins and tsitsikammamines, while the second produces makaluvamines (Kalinski *et al.* 2019). Furthermore, the relationship between the sponges and their microbial symbionts as the source of the bioactive compounds is being investigated (Walmsley *et al.* 2012; Matcher *et al.* 2017).

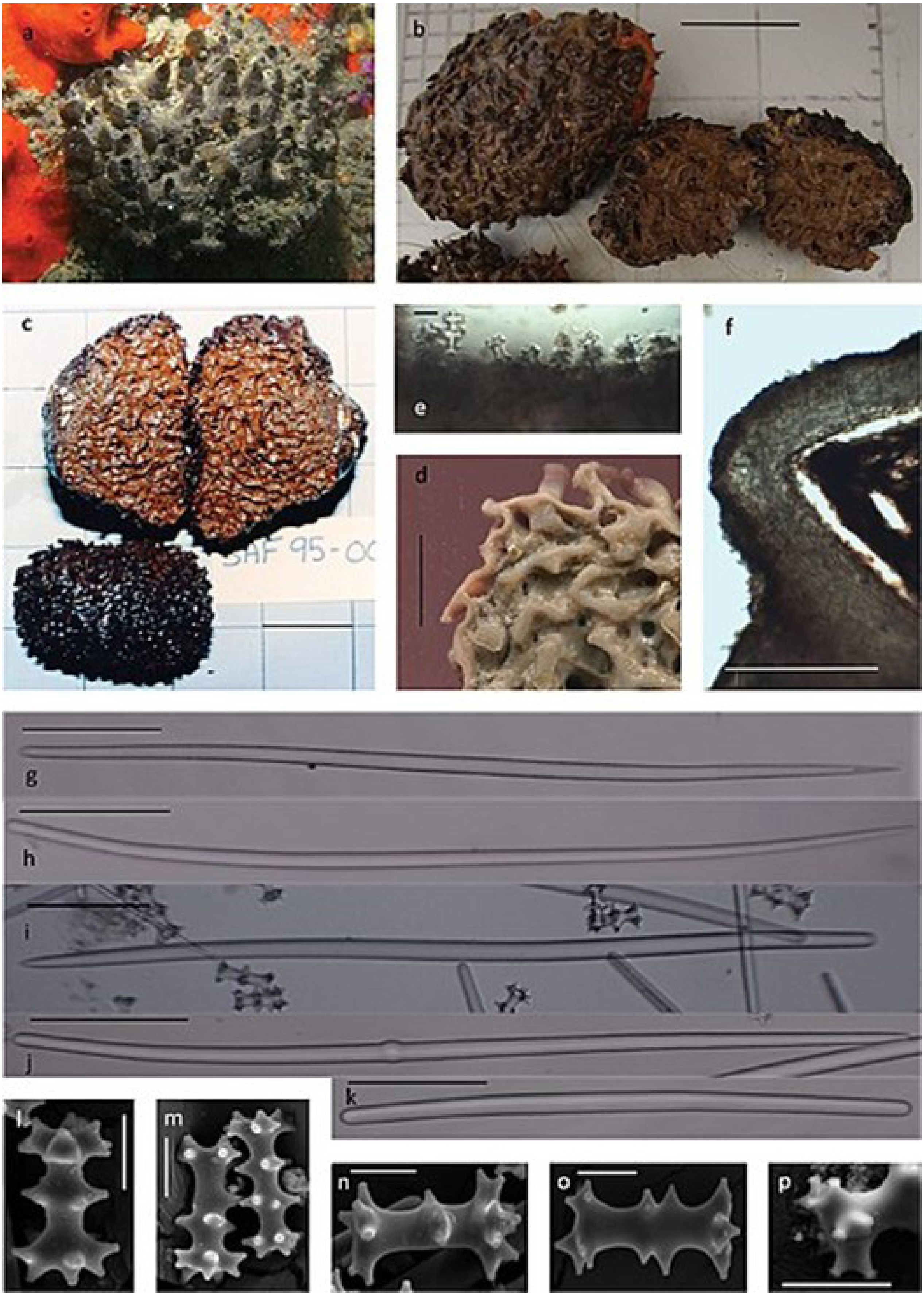

Figure 5: Tsitsikamma favus a in-situ SAIAB 207193 b collected specimens SAIAB 207193 c collected SAF1995-001 d section through preserved specimen SAIAB 141356 e isochiadiscorhabds arrangement on the surface of the ectosome f section of ectosome with underlying choanosome SAIAB 141356 g, h thin sinuous style i large sinuous centrally thickened style j occasionally tylote styles k rare short thick strongyles l–o isochiadiscorhabds SAIAB 207218 SEM p acanthose tubercles SAIAB 207217. Scale bars 5 cm (b, c); 1 cm (d); 1 mm (f); 100 μm (k); 20 μm (l–p). (Source: https://zookeys.pensoft.net/article/32268/list/2/)

A six-year collaborative biodiscovery programme was initiated in Sodwana Bay between 1992 and 1998 between the Oceanographic Research Institute, University of Tel Aviv and the pharmaceutical company Pharma Mar. The corals reefs of Sodwana Bay, situated on the northern coast of KwaZulu-Natal, are the southernmost coral reefs in Africa. They form part of the Indo-Pacific coral reefs which sustain the most diverse marine invertebrate and vertebrate fauna in the world. It follows that this biodiscovery programme has been the most productive to date in the southern African region and has resulted in the discovery of 33 new bioactive compounds and three known compounds. Nine anticancer marine natural products were patented from the Sodwana Bay marine biodiscovery programme, most notably hemiasterlin which together with two synthetic analogues are in clinical development (Talpir *et al.* 1994) (Table 1) (Davies-Coleman and Sunassee 2012). Interestingly, only three invertebrate phyla *viz.* Porifera (sponges), Tunicata (ascidians) and Cnidaria (soft corals) have provided 70%, 21% and 9% respectively of the bioactive secondary metabolites isolated from the invertebrates collected from this area (Davies-Coleman 2005).

Over the period 1994-1995, a large-scale collection of 336 different marine invertebrates was made from three locations along the southern African coast - Aliwal Shoal, Ponto do Ouro and the Tsitsikamma National Park, as part of a collaborative programme between Rhodes University, Scripps Institution of Oceanography and SmithKline Beecham (now GlaxoSmithKline). Despite a significant investment by SmithKline Beecham into the establishment of a sustainable marine biodiscovery research initiative in South Africa, no products were patented from this two-year programme (Davies-Coleman and Sunassee 2012). The extracts were returned by SmithKline Beecham to Rhodes University in 1996 and are now housed at the South African Institute for Aquatic Biodiversity (SAIAB) and continue to be analysed.

Another collaborative initiative between Rhodes University, Scripps Institution of Oceanography and Bristol Myers Squibb (2000-2003) enabled the first large-scale SCUBA collection of marine ascidians in Algoa Bay, South Africa. A new species of ascidian, *Lissoclinum mandelai* was discovered from this collection and sub-milligram quantities of mandelalides A–D were isolated (Sikorska *et al.* 2012). Mandelalides A and B exhibited potent cytotoxicity against lung cancer cells and concerted efforts to synthesise the bioactive compounds followed. While the chemical structure of mandelalide A has now been unequivocally established, enabling synthetic production, the synthetic analogue has shown negligible cytotoxicity against cancer cell lines. According to Davies-Coleman and Veale (2015) potential future drug development interest in the synthetic analogue will only resume if conflicting cancer cell cytotoxicity data reported for naturally-occurring and synthetic mandelalide A can be explained.

A partnership between Rhodes University and the NCI (1998-2012) further contributed to the building of resource bases of South African marine invertebrate extracts in South Africa and the US respectively. A concentrated effort to find new potential anticancer compounds in Algoa Bay between 1998-2000 resulted in the collection of over 300 marine invertebrates. The NCI collection was part of a worldwide collection of plant and marine organisms for their Program for Natural Product Discovery under the Natural Products Branch. The NCI has a Memorandum of Understanding (MoU) with Rhodes University signed in 1998 and the collection was undertaken in partnership with the Coral Reef Research Foundation based in Palau, which has served as the NCI marine organism collection contractor for 22 years, starting in 1992. No new compounds with significant anticancer activity were found from the South African collection. The deposit of extracts prepared from these invertebrates in the NCI's natural product repository has provided access to these extracts by research groups outside of South Africa (Davies-Coleman and Sunassee 2012). Research groups interested in accessing the extracts are required to sign an MTA with the NCI which stipulates that in the event of commercial interest, a benefit sharing agreement must be negotiated with South Africa.

A random screening of 968 marine invertebrate extracts, collected from seven different benthic marine environments around the world, afforded only one extract that showed bioactivity against the Methicillin-resistant *Staphylococcus aureus* bacteria. The extract was from the South African sponge *Topsentia pachastrelloides* with two known metabolites, cis-3,4-dihydrohamacanthin B and bromodeoxytopsentin, the most active compounds (Table 1). While these compounds show potential for antibiotic drug development poor *in vivo* antibacterial activity is hindering progress (Davies-Coleman and Veale 2015).

3.2.3 J. Craig Venter Institute

The J. Craig Venter Institute (JCVI) undertook a two-year genome sampling expedition from 2004 to 2006, the Sorcerer II Global Ocean Sampling Expedition, with the goal to evaluate the microbial diversity in the world's oceans using genomic sequencing tools and techniques (JCVI, n.d. a,b). The purpose was to understand how ecosystems function and to discover new genes of ecological and evolutionary importance. Seawater samples of 200 litres were taken every 200 miles as the vessel circumnavigated the globe. Filtered samples were frozen and later extracted and analysed at the JCVI laboratories with all genomic data (>60 million new genes) stored on GenBank and CAMERA (Community Cyberinfrastructure for Advanced Marine Microbial Ecology Researcher and Analysis), a new database for metagenomic data developed by University of California San Diego. The JCVI state that they will not seek any patents or other intellectual property rights on the genomic sequence data, however the data are freely available on GenBank for anyone to access and innovate from. South African waters were sampled in 2005 as part of the Sorcerer II expedition, prior to the implementation of Bioprospecting, Access and Benefit Sharing (BABS) Regulations in 2008. Thus, permits to collect samples were not obtained from South African authorities, with the vessel likely granted permission to enter South African waters and conduct research via diplomatic channels through the Department of International Relations and Cooperation (Interview 14, DFFE, 4th May 2021). It is unknown whether metadata giving source co-ordinates were uploaded together with genetic sequence data.

3.2.4 Patents

Table 1 provides a summary of the 28 naturally occurring South African marine natural products submitted for patent registration, principally by the National Cancer Institute and Pharma Mar. Secondary metabolites from the tube worm *Cephalodiscus gilchristi* (cephalostatins 1-9), the ascidian *Lissoclinum mandelai* (mandelalides A–D) and the sponge *Topsentia pachastrelloides* (cis-3,4-dihydrohamacanthin B & bromodeoxytopsentin) show the most promise for new drug development. Given the problem of obtaining sufficient supplies of the bioactive compounds for further drug development, the secondary metabolites from these three South African marine invertebrates have been the subject of concerted synthetic programs geared towards producing sufficient amounts of either the natural product or potentially more bioactive analogues, for detailed biological and *in vitro* studies (Davies-Coleman and Veale 2015). However, to date there has been limited success.

The Sodwana Bay sponge *Hemiasterella minor* was discovered to produce hemiasterlin which kills cancer cells at low concentrations. This compound was later rediscovered in a Papua New Guinea sponge and has subsequently been the focus of much research. Multiple derivatives have been developed for use in antibody drug conjugates, affinity probes and tubulin isotype screening most notably by companies in China, Japan and Germany. Two synthetic analogues are in clinical development for use as "warheads" directed to cancer tumours by antibodies (Newman 2021).

Table 1: Patents of naturally occurring marine natural products from South African biodiversity (Source: WIPO PATENTSCOPE)

Naturally occurring compounds	Marine organism	Patents	Institution	Date published	Status
Cephalostatins 1- 4	*Cephalodiscus gilchristi* (tube worm)	US4873245 WO1989008655	Arizona State University/National Cancer Institute	10/10/1989 21/09/1989	Application Application
Cephalostatins 5 & 6	*Cephalodiscus gilchristi* (tube worm)	US5047532	Arizona State University/National Cancer Institute	10/09/1991	Application
Cephalostatins 7-9	*Cephalodiscus gilchristi* (tube worm)	EP0608109 CA2113658 US5583224 JP1995070131 MX-PA/a/1994/000528	Arizona State University/National Cancer Institute	27/07/1994 20/07/1994 10/12/1996 14/03/1995 01/10/1994	Application Application Application Granted
*Spongistatin 4 & 6	*Spirastrella spinispirulifera* (sponge)	US5328929 EP0632042 CA2126911 JP1995145050 MX-PA/A/1994/005002	Arizona State University/National Cancer Institute	12/07/1994 04/01/1995 03/01/1995 06/06/1995 01/01/1995	Application Application Granted Granted
*Spongistatin 5, 7, 8 & 9	*Spirastrella spinispirulifera* (sponge)	EP0634414 US5393897 CA2126910 JP1995157428 ES2123714 MX-PA/a/1994/004999 DE000069412551 DK0634414	Arizona State University/National Cancer Institute	18/01/1995 28/02/1995 03/01/1995 20/06/1995 16/01/1999 01/01/1995 04/02/1999 25/05/1999	Granted Application Granted Granted Granted Granted Granted
**Hallistatin 1	*Phakellia carteri/ Stylissa carteri* (sponge)	CA2113655 US5426194 JP1994279451 EP0608108 MX-PA/A/1994/000532	Arizona State University/National Cancer Institute	20/07/1994 20/06/1995 04/10/1994 27/07/1994 01/09/1994	Application Application Granted Application
**Hallistatin 2	*Phakellia carteri/ Stylissa carteri* (sponge)	US5352804 JP1994279450 CA2113657 EP0608110 MX-PA/a/1994/000533	Arizona State University/National Cancer Institute	04/10/1994 04/10/1994 20/07/1994 27/07/1994 01/09/1994	Application Granted Application Application
Antheliatin & Zahavin A & B	*Anthelia glauca & Alcyonium aurea* (soft coral)	WO1996032388 AU1996053389	Pharma Mar	17/10/1996 19/12/1996	Application Application

Naturally occurring compounds	Marine organism	Patents	Institution	Date published	Status
Sodwanone A, G & H	*Axinella weltneri* (sponge)	WO9701334 AU1996062364	Pharma Mar	16/01/1997 20/03/1997	Application Application
Geodiamolide TA & Hemiasterlin	*Hemiasterella minor* (Kirkpatrick) (sponge)	US5661175	Pharma Mar	26/08/1997	Application
Halitulin	*Haliclona tulearensis* (sponge)	WO0020411 US6635656 AUS1999062170 CA2346865 EP1119565 JP2002526540 MXPA/a/2001/003624 KR1020010093776	Pharma Mar	13/04/2000 21/10/2003 15/06/2000 13/04/2000 01/08/2001 20/08/2002 05/06/2002 29/10/2001	Application Granted Application Application Application Application Application
Cis-3,4-dihydrohamacanthin B & Bromodeoxytopsentin	*Topsentia pachastrelloides* (sponge)	WO2016023106	University of British Columbia	18/02/2016	Application
Other patents related to marine biotechnology					
Pseudoalteromonas, Shewanella, Cryptococcus & Debaryomyces spp.	*Haliotis midae* (abalone)	ZA200406777	University of Cape Town	31/08/2005	Granted
Beta-glucuronidase	*Haliotis midae* (abalone)	EP2250192 US20110077209 ITMI20080357 WO2009109359	ABC CO S.R.L.	17/11/2010 31/03/2011 05/09/2009 11/09/2009	Granted
Protein or glycoprotein	*Haliotis midae* (abalone)	US20110077209 ITMI20080357 EP2250192 WO2009109359	Di Berardino Luigi ABC CO S.R.L. Brenna Oreste Vittore	31/03/2011 05/09/2009 17/11/2010	Granted
Debaryomyces hansenii & Vibrio midae (probiotic microorganisms for feed)	*Haliotis midae* (abalone)	WO2014115112	CSIR University of Cape Town	31/07/2014	Pending
Vibrio midae SY9 (probiotic feed)	*Haliotis midae* (abalone)	AU2019416897 GB2594430 WO2020136574 KR1020210106544 CN113473867	University of Cape Town	02/07/2020 03/11/2021 02/07/2020 30/08/2021 01/10/2021	Pending
Vibrio midae SY9 (probiotic feed)	*Haliotis midae* (abalone)	GB2580310 WO2020136575 GB2594870	University of Cape Town	22/07/2020 02/07/2020 10/11/2021	Pending

* Samples collected from off the Southeast Coast of Africa, location non-specific. Spongistatin 1 samples from Republic of Maldives.
** Samples collected from the Western Indian Ocean, location non-specific. Species recorded around Sodwana Bay, iSimangaliso Wetland Park.

3.3 CURRENT BIODISCOVERY, BIOTECHNOLOGY AND INTERNATIONAL ACTIVITIES

Local scientists unequivocally agree that given South Africa's complex and unique marine environment there is excellent potential for marine biodiscovery. However, it remains that much is not known about the natural product diversity or biomedical potential of the vast and uniquely diverse intertidal and benthic marine invertebrate populations occurring off the country's coastline. Activities have generally been confined to the marine invertebrate communities residing off more accessible coastal areas including the Cape Peninsula, Tsitsikamma National Park, Algoa Bay, Coffee Bay, Aliwal Shoal and Sodwana Bay. Most sampling is by SCUBA or Remotely Operated Vehicle at depths of less than 50 m. While offshore (>50 m) and deep-sea (>200 m) biodiscovery is considered to hold significant potential, Sink *et al.* (2021) highlight that local research in these depths to date has focused on important fisheries resources and oceanography. Significant scientific and technological constraints exist and there is an urgent need to increase deep-sea capacity and expertise to realise any biodiscovery potential. In addition to pharmaceutical biodiscovery, marine resources are increasingly of interest for supplements, cosmetics, probiotics in animal feed and agricultural growth enhancers (Skowno *et al*. 2019).

3.3.1 Pharmaceutical biodiscovery in South Africa

"The fact that we have unique fauna and flora generates the potential to have unique microorganisms associated with it and thus unique compounds ... A lot of work still needs to be done along the South African coastline in terms of microorganisms and biodiscovery"
(Interview 6, SA scientist, 6th December 2020)

The biosynthesis of marine natural products is not random, and the chemical structures of the major natural products usually reflect family and genus structural generalities and species specificity. However, studies have shown the unexpected occurrence of natural products with almost identical chemical structures in two different marine phyla. This points to a shared microbial endosymbiont primary producer of the natural product(s), as opposed to random convergent evolution of secondary metabolic pathways in phyletically disparate marine organisms (Davies-Coleman *et al.* 2019). Therefore, there has been a global shift in marine biodiscovery research towards undertaking microbial community analyses together with metagenomic searches for microbial biosynthetic gene clusters that may be responsible for producing the bioactive compounds.

In line with this shift, since the 2000s research in South Africa has expanded from the discovery of bioactive compounds from marine invertebrates to incorporate an investigation of associated symbiotic microbial communities. In addition to invertebrates and associated microbes, there is also growing interest in marine microbes found in marine sediments, with a focus on actinobacteria. However, isolating microbes and optimising growth conditions to get sufficient quantities of an interesting natural product for chemical analysis is challenging. Therefore, there is also growing emphasis on research that provides a greater understanding of the gene clusters and pathways required for the laboratory synthesis of natural products and developing strategies to use this information to advance biodiscovery.

"Even with microbiology, a lot of marine bacteria require significant optimisation of the growth conditions in order to produce these compounds. Microbiologists will tell you they've got the answers, my experience is theoretically yes, but realistically we haven't reached the point where we're able to produce large amounts of material to significantly push it forward"
(Interview 1, SA scientist, 16th December 2020)

Interesting compounds can be found using classical natural product chemistry, now aided by chemoinformatic tools such as mass spectrometry based molecular networking, or via the use of genome scanning to discover biosynthetic gene clusters that may direct the production of novel metabolites. Once potent and selective activity of a novel compound is identified, it must be isolated following which its bioactivity is verified and the mechanism of action of the molecule is determined. At this point, a medicinal chemistry approach may optimise and facilitate larger scale production before eventually selecting compounds for preclinical and clinical trials (see Figure 6 for a summary of the drug development pipeline) (Sigwart *et al.* 2020). In South Africa there exists an active research community in taxonomy, marine natural products, microbiology, microbial genomics, natural product and pharmaceutical chemistry (See Table 2 for overview of current research activities).

Table 2: Overview of marine biodiscovery and biotechnology research programmes in South Africa

Institution	Department	Focus
Rhodes University	SARChI Chair in Marine Natural Products Research, Department of Biochemistry and Microbiology	Anticancer, antivirals and antibiotics. Pre-existing collections are being retrospectively analysed for compounds with the development of metabolomic analysis capacity. Analysis of new collections of sponges and ascidians from Algoa Bay, St Francis Bay, Plettenberg Bay and KwaZulu-Natal.
University of the Western Cape	SARChI Chair in Microbial Genomics, Institute for Microbial Biotechnology and Metagenomics	Microbial biotechnologies for a range of industries, including marine biodiscovery. Specific interest in bridging the gap between fundamental research and commercial application. Isolating and DNA sequencing of microorganisms to investigate the organisms, compounds, and pathways producing bioactivities.
University of the Western Cape	School of Pharmacy	Chemistry of marine natural products from marine algae, invertebrates and microorganisms. Chemoinformatics and molecular networking. Partnerships with CPUT and Oceans and Coasts.
Cape Peninsula University of Technology	Applied Microbial and Health Biotechnology Institute	Antibiotics and oxidative enzymes. Mining actinobacterial compounds isolated from sponges and sea squirts collected from Algoa Bay and Marion Island (MTA with Rhodes). Assessing marine sediments for actinobacterial diversity using next generation sequencing and screening approximately 350 isolates for antibiotic activity and enzyme production.
University of Cape Town	Actinomycete and Antibiotic Research Unit	Antibiotics. Investigating the diversity of actinobacteria as a source of novel antimycobacterial molecules with a focus on determining actinobacterial biodiversity and taxonomy.
University of Cape Town	Marine Biotechnology	Probiotics, vaccines. Development of vaccines against emerging infectious diseases of farmed kob. Microbial probiotics for farmed abalone that increase disease resistance and growth rate both in the hatchery and grow-out stages of the farming process.

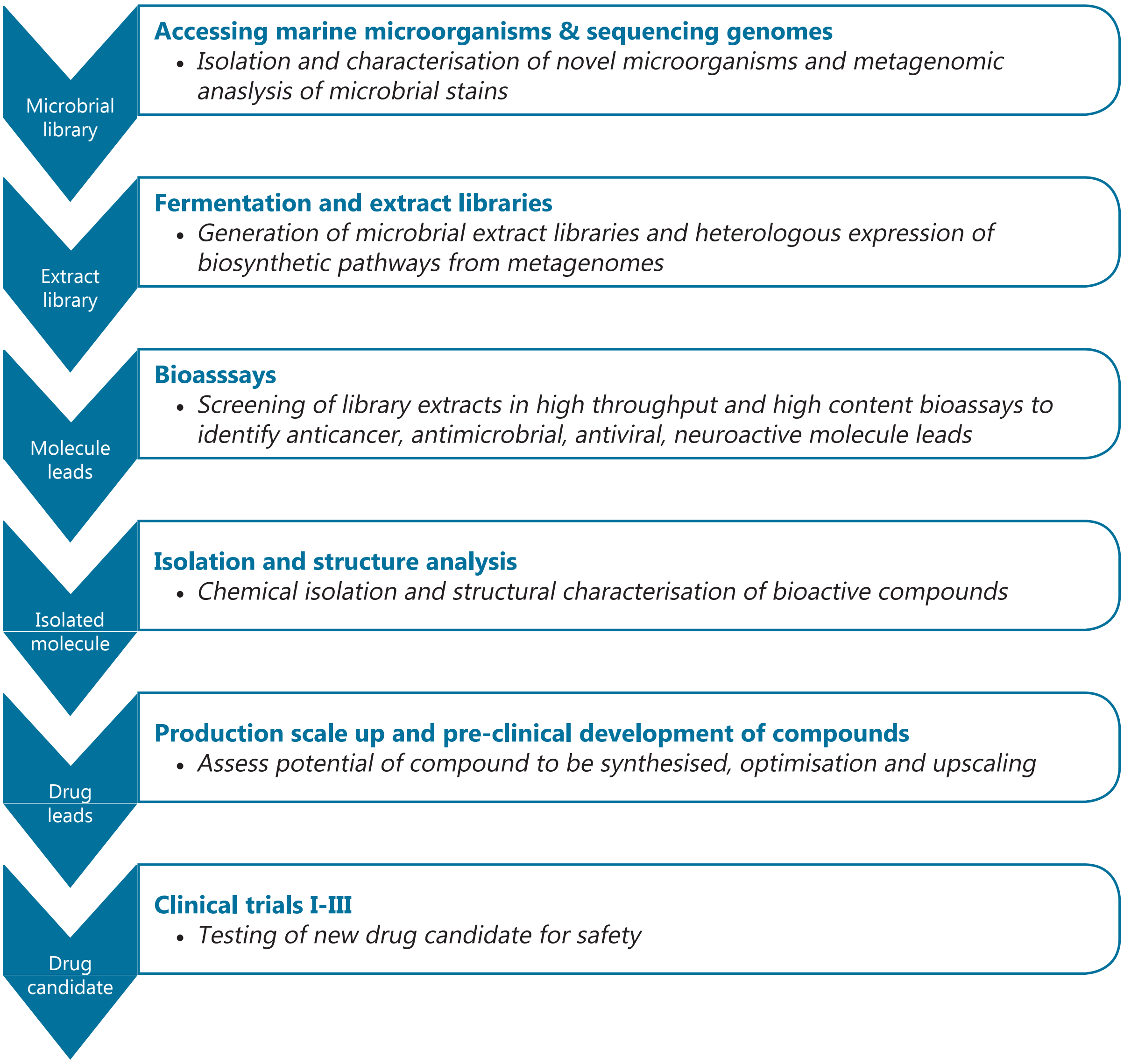

Figure 6: Drug development pipeline from marine microorganisms (Sourced and adapted from the PharmaSea project)

With new understandings of microbial endosymbiosis, it is thought that while marine invertebrates may exhibit location-specific diversity, the associated microbial flora may exhibit connectivity across geographies. Such patterns could negate the importance of South Africa as a unique site for biodiscovery. A great deal of research on the biogeography of marine microorganisms has been carried out, but many unknowns persist, and more research is needed to elucidate and understand the composition of marine microbial communities (Hunter-Cevera 2005; Martiny *et al.* 2006). Further, the degree to which the processes structuring macroorganismal communities also structure microbial communities, and whether parallel processes result in parallel biodiversity patterns remains unclear (Barberán *et al.* 2014).

"We don't have the detail to be able to say what a particular sponge's microbial flora is going to look like in the South Atlantic or in the Equatorial region. If it's the microbial flora that dictates what's produced then it's not clear how the geography would affect it" (Interview 12, UK scientist, 3rd March 2021)

In addition to marine fauna, seaweeds are also an excellent source of biologically active secondary metabolites and have been shown to exhibit a wide range of therapeutic properties, including anticancer, antimicrobial, antioxidant, anti-inflammatory and antidiabetic activities. The potential of using seaweed-derived bioactives to treat chronic diseases and antibiotic resistance is expected to be a major frontier in pharmaceutical research (Collins *et al.* 2016). In South Africa, Mabande (2018) found antimicrobial activity of crude factions extracted from *Plocamium* sp. and *Stypopodium multipartitum* to be excellent, however the isolated compounds showed limited activity. Given the long tradition of diverse use of marine plants by local communities around the world, including South Africa, their increasing investigation by the scientific community also raises questions around the links between marine biodiscovery, ILK and access and benefit sharing.

3.3.2 Marine genetic resources for biotechnology and biotrade in South Africa

Another stream of research in South Africa is concerned with the use of marine biotechnology for the optimisation of aquaculture, specifically abalone (*Haliotis midae* L.) (Bolton *et al.* 2013). South Africa produces over 1,000 tons of cultured abalone per annum and has been described as the largest producer outside Asia (Britz *et al.* 2009). Macey and Coyne (2005) isolated *Vibrio midae* SY9 from the digestive tract of *H. midae* and showed that when administered as a cocktail of three probiotic strains in a formulated feed, *V. midae* SY9 increased the growth rate of farmed abalone by up to 40% and improved the survival and immunity of animals challenged with the pathogen *Vibrio anguillarum*. The bacteria were originally isolated from the digestive tract of farmed abalone and cultured to upscale production. The probiotic feed is now patented and a new patent for use of the probiotics in abalone hatcheries is in process (Table 1).

Under biotrade (see Box 1 for definition), marine algae are harvested for aquaculture feed products, phycocolloids (alginates and algar) and plant growth enhancers. In South Africa, approximately 850 species of algae have been described, accounting for nearly 10% of species globally with a third endemic to South Africa. On average 10,000 tons of kelp is harvested annually, predominantly *Ecklonia maxima* for alginate, algar, abalone feed and agricultural liquid plant growth enhancer. *Ulva* spp. is a major aquaculture product with approximately 2,000 tons per year produced in integrated land-based systems with abalone - both for feed and for recirculation of wastewater (Rothman *et al.* 2020). There is also growing interest in algae for cosmetics and nutrition. A survey found that of 549 retail products that contain South African indigenous products, at least 15 products contained marine resources (DEA 2015).

BOX 1: Definition of biotrade and biodiscovery

BIOTRADE – the commercial collection, processing and sale of specialty products derived from biodiversity, usually for the natural cosmetic and personal care, functional food, botanical medicine and other sectors relying on the sourcing of raw materials. Biotrade often uses traditional knowledge in products and marketing, and some biotrade companies focus on sustainability and equity issues, and products may be certified.

BIODISCOVERY – the collection of and research on samples of biological resources in order to discover genetic information or biochemicals of value. Primarily the pharmaceutical and biotechnology sectors, but also including crop protection, food and beverage, and others. The use of "digital sequence information" – or genetic sequence data –increasingly spans all industrial and commercial sectors.

3.3.3 Marine genetic resources for international research

According to records in the Access and Benefit sharing Clearing-house of the CBD several export permits have been issued for scientific investigations on South African marine biodiversity by international institutions, however, most of the detail of the permits are considered to be confidential and are not available to the public.

- marine molecular ecology (University of Oldenburg, in partnership with Nelson Mandela University and University of Johannesburg)
- e-DNA sequencing of marine samples (University of Oldenburg in partnership with Nelson Mandela University)
- marine scientific research using collected water, phytoplankton, micro- and mesoplankton samples to be conducted onboard the German research vessel *SONNE* in South Africa territorial waters between 13-19 September 2021 (University of Hamburg)
- unspecified research (University of Oldenburg in partnership with University of Fort Hare)
- unspecified research (University of Hamburg)

3.4 ACCESS TO MARINE GENETIC RESOURCES

Early biodiscovery *in-situ* collections were undertaken via vessel-based trawling and later SCUBA with collections focused on the more accessible coast of South Africa at depths of less than 100 m. Collections prior to the enactment of the Marine Living Resources Act, 1998 were undertaken without formal permitting requirements, however, these collections were mostly done in collaboration with South African researchers with samples lodged in-country. Collection permits are now jointly assessed and issued by the Department of Forestry, Fisheries and Environment (DFFE): Oceans and Coasts branch and Fisheries Management branch on a case-by-case basis according to a scientific process to evaluate environmental impact and risk. Collection permits specify species to be collected, number of specimens, location, permitted transportation and conditions of the permit. Where the application for collection is for biodiscovery purposes, the DFFE: Bioprospecting and Biodiversity Economy branch is also notified.

Samples may be collected from within a Marine Protected Area for non-commercial purposes only and under specified conditions. In the case of iSimangaliso Wetland Park, a Marine Protected Area and UNESCO World Heritage Site, researchers are required to register with the iSimangaliso authority and must obtain an entry permit and sampling permit in addition to a collection permit from DFFE. A similar situation may pertain in other national parks adjoining marine areas. More recently, with interest in actinobacteria and other microorganisms in marine sediments, samples are being collected in the intertidal and subtidal zones with permits for marine sediment samples also issued by Oceans and Coasts.

The primary *ex-situ* marine invertebrate collections in the region are housed at the Iziko South African Museum in Cape Town and comprise some 129,000 records, offering significant coverage of all major marine taxonomic groups. Other, more specialised collections are housed at several other museums and universities around the coast, including the South African Institute for Aquatic Biodiversity[3] (SAIAB) in Makhanda – a National Research Foundation (NRF) National Collection facility – and the KwaZulu-Natal Museum. The SAIAB database is searchable via the Global Biodiversity Information Facility (GBIF)[4]. These *ex-situ* repositories can be accessed for marine biodiscovery by local researchers with a Material Transfer Agreement, and by international researchers with a Material Transfer Agreement and Discovery Phase Export Permit issued by DFFE. An *ex-situ* natural products repository is also held by the NCI, which has a long-standing MoU with Rhodes University. The samples are accessible to external research organisations through either the Open Repository Programme or the Active Repository Programme according to the terms and conditions set out in the Policy for the Distribution of Materials from the Natural Products Repository, including a Material Transfer Agreement with the NCI[5].

More recently there has been an initiative by the Department of Science and Innovation to establish national biobanks and databases for non-plant collections. Through the provision of nationally and internationally accessible biobanks and databases the initiative seeks to promote research, increase understanding of marine biodiversity and improve efforts to conserve it by providing baseline data.

3.5 COLLABORATIVE RESEARCH AND INTERNATIONAL PARTNERSHIPS

Multidisciplinary collaboration is an essential feature in the effective discovery and development of novel drugs. The discovery of promising bioactive molecules typically involves close collaboration with biologists, however, the actual compound isolated from the natural source is rarely suitable for development into an effective drug or agrochemical product. The lead molecule can form the basis for further chemical or biochemical modification but the structural optimisation process generally requires significant input from biochemists, medicinal and synthetic chemists. Such pre-clinical development also always requires close collaboration with pharmacologists and toxicologists to determine the optimal pharmacodynamic and toxicological parameters necessary for advancement of the agent into clinical trials with human patients (Cragg *et al.* 2012).

As such, most scientists working in the marine biodiscovery space in South Africa are part of local and international research partnerships. Locally, the partnerships create multidisciplinary research teams to work on different aspects of the discovery pipeline. The partnerships also enable the sharing of technology and resources with, for example, one institution undertaking collections and taxonomy, another offering molecular networking, and others genetic sequencing.

Davies-Coleman and Sunassee (2012) highlight that the relatively rapid advances made in South African marine biodiscovery can be attributed, in no small measure, to the involvement of international partners such as the National Cancer Institute, Scripps Institution of Oceanography and SmithKline Beecham. In earlier years, partnerships often focused on capacity development through staff and student knowledge exchange and training, for example at the NCI. Local researchers now have the capacity to carry out the discovery phase, yet international collaborations continue to be integral to marine biodiscovery in South Africa as they enable

[3] https://www.saiab.ac.za/saiab-collection-facility.htm
[4] https://www.gbif.org/dataset/1aaec653-c71c-4695-9b6e-0e26214dd817
[5] https://global.oup.com/us/companion.websites/fdscontent/uscompanion/us/static/companion.websites/9780199965762/update/Appendix_A.pdf

researchers to be part of strategic networks that bring together complementary expertise in the pharmaceutical pipeline. Thus, the focus of partnerships is to create consortia with specialised expertise and infrastructure required for the whole pipeline, together with opportunities for expanding research capacity and building critical mass in marine biodiscovery research. Increasingly, South African researchers are looking for partnerships towards interdisciplinarity and symmetrical participatory structures to enable innovative, locally relevant research.

"There are some things South Africans do a lot better and then there are some things the UK does a lot better (Interview 10, SA scientist, 25th November 2020).

"It's not about us sending people to the UK to get trained. It's about us working together on each side and training where it's required" (Interview 7, SA scientist, 1st December 2020).

A key challenge in South Africa is the lack of resources to optimise promising compounds to become potential drugs that can go into commercialisation. The research and development journey of new drugs that make it to market costs around £1.15bn with the most expensive part of drug development being the pre-clinical and clinical work (Torjesen 2015). Owing to the extensive work done on drug development for HIV and AIDS, researchers have highlighted that South Africa has excellent infrastructure but lacks funding and a coordinated strategy for drug development. Local researchers thus benefit from partnerships with potential access to equity partners. For example, both the PharmaSea and South Africa-UK Antibiotic Accelerator Initiative projects (see Boxes 3 and 4 below) are linked to spinout companies from the lead institutions that enable opportunities to "*centralise IP and equity interests into a single place*" for ease of progressing an existing interesting compound to clinical trials which grant funders are not able to do (Interview 12, UK scientist, 3rd March 2021).

Research partnerships are often built over the long-term, for example through PhD supervision and subsequent mentoring or introductions through other colleagues, resulting in trust, transparency and reciprocity. "*For us, the relationship was built on somebody that you know and trust and then building on that to get materials that are exciting for research*" (Interview 13, UK scientist, 19th February 2021). A successful partnership will often result in continued collaboration for many years beyond the completion of a project, thereby providing significant long-term benefits (see Box 4 below) and opportunities to build and maintain sustainable infrastructure.

BOX 2: Newton Advanced Fellowship

A collaboration between the University of Cape Town and the University of Aberdeen which began in November 2016 was awarded £96,000 for a three-year period. This included a component of £15,000 per year for research support to cover costs for consumables, equipment, Ph.D. studentships and staff.

The main aim of the project was to screen, isolate and identify novel bioactive natural product molecules from an existing collection of about 100 actinomycetes to discover new and/or more effective antitubercular agents.

The project produced promising avenues of research with the isolation and identification of at least six compounds. Further investigations of these different strains have shown promising biological activity against tuberculosis.

Despite the merits of these partnerships, Kyeremeh *et al.* (2020) highlight that funding models to support North-South research collaborations are often non-renewable and thus have too short a timeframe for biodiscovery research. As a result, funding models tend to favour new partnerships and research priorities of the host funding bodies, usually based in the Global North.

BOX 3: South Africa-UK Antibiotic Accelerator Initiative (SA-UK AAI)

The SA-UK AAI is a three-year partnership (2020-2022) between Rhodes University, University of Plymouth, St. Andrews University and Leeds University to identify potential compounds from pre-existing South African and UK chemical libraries. Each partner will do their own biodiscovery on their own samples and "*share the information and technology that we develop*" (Interview 7, SA scientist, 1st December 2020). Funded by the South African Medical Research Council and the Newton Fund, anticipated benefits of this partnership include:

1) Putting systems, capacity and resources in place that can have a legacy in natural product research in South Africa.
2) Access to expertise and technology for synthesis and optimisation of compounds not readily available in South Africa.
3) Potential commercialisation through investment and industry partners in the UK.

The project is unique and ambitious in that it is commercially focused with the aim to have a small collection of compounds with commercial potential by the end of the three years. In the context of the SA-UK AAI, traceability is a key component with a well-structured database in place for tracking of all activities and relevant metadata.

BOX 4: PharmaSea

PharmaSea (www.pharma-sea.eu) was a large-scale, five-year (2012-2017) collaborative project to collect and screen samples to discover novel products for the treatment of infections, inflammation and neurodegenerative diseases. The project was backed by more than €9.5 million of EU funding and brought together 24 partners from 13 countries from industry, academia and non-profit organisations. The project focused on the biodiscovery, development and commercialisation of new compounds from marine organisms with a focus on underexploited marine phyla of cultivable microorganisms. It aimed to achieve optimised and sustainable production of relevant biomass and high added-value compounds for pharmaceutical, nutraceutical and cosmeceutical applications, and to overcome some of the major bottlenecks in the drug discovery pipeline (Jaspers *et al.* 2016).

PharmaSea, led by Aberdeen University, partnered with the Institute for Microbial Biotechnology and Metagenomics at the University of the Western Cape. Through PharmaSea, funding was obtained to develop a large collection of microorganisms isolated from South African marine invertebrates. The institute continues to undertake screening for activity with a focus on anti-neurodegeneratives and antimicrobials and is actively seeking partners or projects to further investigate the collection as there is enormous potential for biodiscovery applications, in the medical industry and otherwise. A key outcome of the partnership was the building of critical mass in marine biodiscovery research in South Africa through training postgraduate students. The additional benefit of PharmaSea was continued collaboration for 6+ years beyond the completion of the project creating significant long-term benefits.

3.6 REGULATORY AND INSTITUTIONAL FRAMEWORKS

3.6.1 Environmental policy and legislation

South Africa is a party to the CBD and NP and has implemented legislation with respect to access to biological and genetic resources and benefit sharing. In relation to other blue economy initiatives such as fisheries, aquaculture and mining, marine biodiscovery has received little attention at a national level. A key challenge is how best to leverage legislation and other mechanisms for equitable research partnerships in biodiscovery research and development given the current inequitable geography of technology and funding for research. In forging access and benefit sharing arrangements relating to marine genetic resources, consideration needs to be given to capacity building, technology transfer, funding for research and biodiversity conservation, authorship, IPRs and ownership of ILK.

ABS measures in South Africa include the establishment of a national competent authority, national focal point, clearing house, and legislative and administrative procedures. The Department of Forestry, Fisheries and Environment (DFFE) is the national focal point and clearing house for ABS in South Africa. All biodiscovery is regulated through the National Environmental Management: Biodiversity Act, Act No. 10 of 2004 (NEMBA)[6] by a notification and permit system under the Bioprospecting, Access and Benefit Sharing (BABS) Regulations of 2008 and its 2015 amendments (Table 3). However, in terms of the Constitution, marine resources are a national competence and are regulated by the Marine Living Resources Act No. 18 of 1998. All permits to research and use marine resources are thus administered by the Branches: Oceans and Coasts and Fisheries Management in the DFFE through a scientific process of evaluation. Applications for research within provincial reserves and national marine protected areas (MPAs) must be accompanied by proof of registration and approval from the relevant Managing Authority prior to an application to DFFE. If the same organisms exist outside of the MPA applicants are encouraged to rather collect in these areas.

All bioprospecting permits are lodged with the publicly accessible Access and Benefit sharing Clearing-house of the CBD[7]. However, most of the detail of the permits is considered to be confidential and not available for public purview. NEMBA and associated regulations are currently under review.

[6] The National Environmental Management: Biodiversity Act, Act No. 10 of 2004 (NEMBA) defines an indigenous biological resource as a resource that includes any living or dead animal, plant or other organism of an indigenous species, their derivatives and genetic material, gathered from the wild or accessed from any other source, including cultivated, bred or kept in captivity, or cultivated or altered in any way by means of biotechnology (RSA 2004).

[7] https://www.environment.gov.za/projectsprogrammes/bioprospectingaccess_benefitsharing_babs_clearinghouse

Table 3: Environmental policy and legislation relevant to marine biodiscovery in South Africa

ENVIRONMENTAL POLICY AND LEGISLATION		
INSTRUMENT	**AIM**	**RELEVANT INSTITUTION**
CONSTITUTION		
Constitution of the Republic of South Africa (No. 108 of 1996)	Conservation and ecological sustainability are given prominence in the Bill of Rights. The Constitution does not vest ownership of genetic resources in the State.	Marine resources are specified as a national competence
NATIONAL ACTS		
National Environmental Management Act (No. 107 of 1998)	Gives legal effect to the Constitution and to the White Paper on Environmental Management Policy. Sets in place procedures and mechanisms for cooperative governance and regulates environmental impact assessments.	DFFE
National Environmental Management Act: Biodiversity Act (No. 10 of 2004)	Regulates the exploration of biodiversity for commercially valuable indigenous genetic and biological resources. Protects the interests of certain stakeholders; outlines the requirements of material transfer and benefit-sharing agreements; establishes the Bioprospecting Trust Fund; and provides for the exemption of certain activities or indigenous biological resources from the legislation.	DFFE are responsible for regulating bioprospecting.
National Environmental Management Laws Amendment Act (No. 14 of 2009 and No. 14 of 2013)	To introduce notification requirements in the discovery phase of a bioprospecting project; to take into consideration knowledge of specific individuals when issuing specific bioprospecting permits; to allow the Director-General or a trustee to manage the Bioprospecting Fund; to allow for the renewal or amendment of a permit.	DFFE
Marine Living Resources Act (No. 18 of 1998)	Provides for the conservation of marine ecosystems, the sustainable use of marine living resources and for orderly and equitable access to such resources. Regulates the collection of marine biological resources.	DFFE
National Environmental Management: Integrated Coastal Management Act (No. 24 of 2008)	To establish a system of integrated coastal and estuarine management to promote the conservation of the coastal environment, maintain the natural attributes of coastal landscapes and seascapes, and to ensure that development and the use of natural resources within the coastal zone is socially and economically justifiable and ecologically sustainable.	DFFE
Marine Spatial Planning Act (No. 16 of 2018)	To provide a framework for marine spatial planning in South Africa, the development of marine spatial plans and the institutional arrangements for the implementation of marine spatial plans and governance of the use of the ocean by multiple sectors.	DFFE and other stakeholders
National Environmental Management Act: Protected Areas Act (No. 57 of 2003)	Provides for the declaration and management of protected areas and promotes sustainable utilisation of protected areas for the benefit of people, as long as the ecological character of the area is preserved.	DFFE
Sea Birds and Seals Protection Act (No. 46 of 1973)	To provide for the control over certain islands and rocks; the protection and the control of the capture and killing, of sea birds and seals; and for the disposal of the products of sea birds and seals.	DFFE
Marine Pollution Act (No. 2 of 1986)	To provide for the application in the Republic of the International Convention for the Prevention of Pollution from Ships.	DFFE

Genetically Modified Organisms Act (No. 15 of 1997)	To provide for measures to promote the responsible development, production, use and application of genetically modified organisms.	Department of Agriculture, Land Reform and Rural Development
NATIONAL REGULATIONS		
Bioprospecting, Access and Benefit Sharing (BABS) Regulations of 2008 and Amendment Regulations of 2015	Regulates bioprospecting in South Africa. National Minister for Forestry, Fisheries and Environment is responsible for issuing bioprospecting and export permits for bioprospecting purposes. Foreigners may only apply for permits jointly with a South African collaborator. Export must be in the public interest. A benefit-sharing agreement may be refused if there is no provision for enhancing scientific and technical capacity to conserve, use and develop biodiversity or to promote conservation.	DFFE
Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) Regulations of 2010	Regulates the import, export and re-export of threatened or protected species listed under the Schedule of the CITES Regulations. Exporters of a CITES-listed species need to apply for a CITES certificate which is issued by the provincial department responsible for conservation, or the national department.	DFFE and provincial departments
Threatened or Protected Species (TOPS) Regulations of 2007	Applies to restricted activities involving specimens of listed threatened or protected species; it provides for the prohibition of specific restricted activities involving specific listed threatened or protected species; and provides for the protection of wild populations of listed threatened species.	DFFE and provincial departments
PROVINCIAL ACTS AND REGULATIONS	Varied, but most regulate biodiversity research and the collection and use of wild species through a permitting system. However, because marine resources are a national competence and are regulated by the Marine Living Resources Act, permitting for marine resource use takes place at a national level. All research activities conducted inside of marine protected areas are required to be registered with and approved by the relevant regulatory authority.	Different provincial conservation agencies and government departments
STRATEGIES		
National Bioeconomy Strategy (2014)	Aims to harness bio-innovation for economic growth and social development in South Africa. Focuses on agriculture, health and industrial application.	Department of Science and Innovation
National Biodiversity Economy Strategy (2016)	Aims to guide the sustainable growth of the wildlife and bioprospecting industries and to provide a basis for addressing constraints to growth, ensuring sustainability, identifying clear stakeholder's responsibilities and monitoring progress.	DFFE

Biodiscovery is differentiated between the Discovery Phase and the Commercialisation Phase. The Discovery Phase is any research on, or development or application of, indigenous biological resources where the nature and extent of any actual or potential commercial or industrial exploitation in relation to the project is not sufficiently clear or known to begin the process of commercialisation. The Commercialisation Phase describes research, development or application of resources with the objective of commercialising them.

Before undertaking any marine biodiscovery research involving any indigenous genetic and biological resources, it is first necessary to submit a Discovery Phase Notification Form to DFFE. This should include details relating to the project including partners and sponsors, biological material to be collected, including species, amount and locality, other permits obtained, including provincial, TOPS (threatened or protected species) and CITES, and where applicable, Prior Informed Consent (PIC) and details of any associated traditional knowledge. The Discovery Phase Notification legally binds the holder to apply for a bioprospecting permit should the project enter the Commercialisation Phase. The Discovery Phase requires an annual status report which covers biological resources collected, research conducted, progress towards commercialisation, patent applications, engagement with industry, patent licensing and transfer of materials.

The BABS Regulations also include biotrade where biological resources are used to produce other products such as phytomedicines and essential oils. Export of any indigenous genetic and biological resources for the purpose of biodiscovery or any other kind of research is regulated under the BABS Regulations and requires an export permit with a Material Transfer Agreement (MTA) and Prior Informed Consent (PIC) and Benefit-Sharing Agreement (BSA) where relevant (Table 4). Approximately 11 Discovery Phase Notifications and five Discovery Phase Export Permits for research on marine genetic resources have been issued (DFFE, pers. comm., 8th December 2020).

Activities under the Commercialisation Phase may include the filing of a full patent application in South Africa or elsewhere, obtaining intellectual property rights, commencement of clinical trials and product development, including market research, and multiplication of indigenous biological resources through cultivation, propagation or cloning to develop and produce drugs, complementary medicines, nutraceuticals, industry enzymes, food flavours, fragrances, cosmetics, emulsifiers, oleoresins, colours, extracts, and essential oils. Permit applications for the Commercialisation Phase require PIC, a MTA and a BSA with stakeholders. International researchers must apply for this permit jointly with a South African institution or researchers. Genetic resources are a national competence, thus permission comes from the Minister and bioprospecting permits for marine biodiscovery are jointly issued by DFFE: Bioprospecting and Biodiversity Economy and DFFE: Oceans and Coasts. Currently, one bioprospecting permit for marine biotechnology related to abalone aquaculture has been issued but has not yet entered the commercialisation phase (DFFE, pers. comm., 16th March 2021). Following the issuing of a bioprospecting permit, downstream uses are traced via the annual status update form submitted to DFFE which includes information regarding patenting, commercial use, clinical trials and revenues generated, however scientific publications are not included.

Marine research permits for non-biodiscovery purposes such as taxonomy, phylogenetics, systematics and natural science collections are jointly issued by DFFE: Oceans and Coasts and DFFE: Fisheries Management. For the collection and analysis of samples for marine biodiscovery both a collection permit and a Discovery Phase Notification acknowledgement letter are required.

For export of *ex-situ* material from a province for research the provincial issuing authority must be notified and provided with a copy of the research agreement. Other permits may also be required for the collecting of genetic and biological resources from national parks or nature reserves, including, CapeNature for Western Cape Nature Reserves, SANParks for National Parks, Eastern Cape Parks and Tourism Agency for Eastern Cape and Ezemvelo KZN Wildlife for KwaZulu-Natal Parks.

Table 4: Permitting procedures for biodiscovery in South Africa (Source: www.environment.gov.za/projectsprogrammes/bioprospectingaccess_benefitsharing_babs_clearinghouse)

Activity	Type of permit	Issuing authority
Non-commercial research		
Research other than bioprospecting conducted in South Africa	No bioprospecting permit required but may require a collection and/or research permit from the relevant authority	Relevant province or government agency
Discovery phase of bioprospecting		
Discovery phase of bioprospecting conducted in South Africa	No permit required, notification procedure must be followed	Notify the Minister using prescribed form
Discovery phase of bioprospecting conducted outside South Africa	Discovery phase export permit	Apply to the Minister using the prescribed form for discovery phase export
Commercialisation phase of bioprospecting		
Bioprospecting conducted in and/or outside South Africa	Bioprospecting permit	Apply to the Minister using the prescribed form for bioprospecting

3.6.2 Convention on the Law of the Sea (UNCLOS)

Under UNCLOS, territorial waters extend 12 nautical miles from the baseline beyond which is the Exclusive Economic Zone (EEZ) and the continental shelf that extends 200 nautical miles from the baseline. Within the EEZ or areas of national jurisdiction, states have the exclusive right to explore and exploit all natural resources. South Africa provides for these maritime zones in terms of the Maritime Zones Act, No. 15 of 1994, with any law enforced in the Republic also applying in the internal waters, territorial waters, EEZ and continental shelf. Therefore, under the Maritime Zones Act, the NEMBA and BABS Regulations are applicable to all these zones.

Under UNCLOS, states can apply to extend their continental shelf by 150 nautical miles, affording sovereign rights to states for the mineral and other non-living resources of the sea that are in the subsoil, together with living organisms belonging to sedentary species[8]. The superjacent water above the continental shelf and non-sedentary species are governed by the high seas principle, that is, open to all nations and not subjected to national sovereignty. South Africa has put in an application to extend its continental shelf and has received a recommendation from the Commission for its mainland territory, but is still awaiting a recommendation for the Prince Edward Islands.

Article 240(d) of UNCLOS states, "*Marine scientific research shall be conducted in compliance with all relevant regulations adopted in conformity with this Convention including those for the protection and preservation of the marine environment*". South Africa thus has an obligation under UNCLOS to implement measures to protect the marine environment as it relates to marine biodiscovery. However, under the National Environmental Management Act, marine biodiscovery does not require an environmental authorisation through an environmental impact assessment. Some hold the view that, "*If you remove something out of the ecosystem, the methods you use can cause irrevocable damage, even if it doesn't amount to a large-scale harvest*" (Interview 4, SA legal researcher, 3rd December 2020). Thus, there is concern that while the Marine Living Resources Act is guided by sustainability principles to prevent overharvesting

[8] "Organisms which at a harvestable stage, either are immobile, on or under the seabed, or are unable to move except in constant physical contact with the seabed or the subsoil" (UNCLOS, Article 77).

of marine resources, there is a legal gap around protection of the marine environment from where resources are harvested and the methodologies used. For example, this may include use of extensive light and sound or seabed drilling to obtain microbes from marine sediments which may cause harm to the broader environment.

"Where there's a great deal of silence is: how do we permit, or how do we undertake environmental impact assessment as far as activities pertain in ocean spaces? From a practitioner's perspective, especially the people who desire to undertake activities over there, thought needs to be applied as to what measures will be taken into play or form part of South Africa's international obligations when it comes to protecting the marine environment from such activities" (Interview 3, SA legal researcher, 8th December 2020).

The conservation and sustainable use of marine biodiversity of areas beyond national jurisdiction (ABNJ or BBNJ) is increasingly attracting international attention as scientific research reveals the richness and vulnerability of such biodiversity, particularly around seamounts, hydrothermal vents, sponges, and cold-water corals. At the same time, concerns are growing about the increasing anthropogenic pressures posed by existing and emerging activities such as fishing, mining, marine pollution, and deep-sea bioprospecting. In response, a series of intergovernmental meetings are underway to negotiate the terms of a legally binding BBNJ agreement under UNCLOS. The use of marine genetic resources, capacity building and the transfer of marine technology are key elements of the negotiations.

South Africa is actively involved in the negotiations as a state and as a member of the African Group of Negotiators and G77 and China. In 2015, South Africa chaired the G77 and China and from 2013 to 2016, South Africa co-ordinated the African Group. As a result of holding both positions simultaneously, South Africa was able to significantly influence the groups' agreement on multiples issues. Currently, South Africa is the lead negotiator for the African Group on cross-cutting issues in the negotiations and South Africa's position and that of the African Group remain united. However, within the G77 and China, there is not a unified position, due in part to an absence of strong leadership (Interview 16, DIRCO, 14th December 2021).

South Africa's position includes strong support for the principle of the common heritage of humankind to guide and underpin the new legal regime for the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction. It is argued by South Africa's delegation that the common heritage forms the legal basis for implementing the agreement, without which there will be no obligation for benefit sharing, capacity building or transfer of technology to less wealthy countries. That is, access to BBNJ will remain the privilege of wealthy nations.

The fifth session to negotiate the BBNJ Agreement[9] took place in August 2022 but no consensus was reached and negotiations have been suspended until 2023. The principle of the common heritage of humankind remains contested among states.

3.6.3 Intellectual property

The regulation of innovation from marine biodiscovery is also pertinent to marine biodiscovery. Under the South African Patents Amendment Act, No. 20 of 2005, upon lodging an application for a patent, the applicant is required to disclose whether the invention is based on or derived from an indigenous biological resource, genetic resource, or traditional knowledge or use. If so, the applicant is required to furnish proof in the prescribed manner as to their authority to make use of the indigenous biological resource, genetic resource, or traditional knowledge.

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[9] United Nations General Assembly. 1 June 2022. Further revised draft text of an agreement under the United Nations Convention on the Law of the Sea on the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction.

Table 6: Intellectual property policy and legislation relevant to marine biodiscovery in South Africa

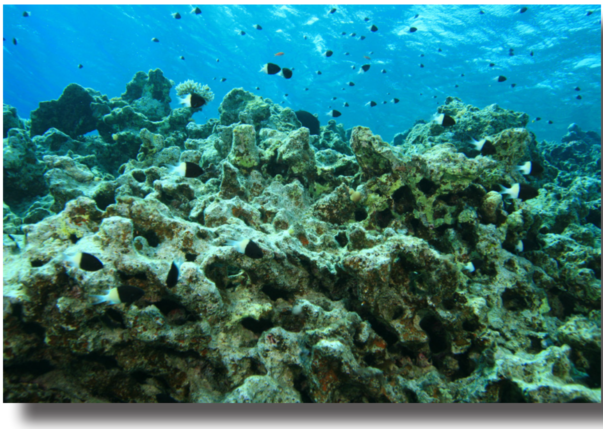
INTELLECTUAL PROPERTY POLICY AND LEGISLATION		
Patents Act (No. 57 of 1978) Patents Amendment Act (No. 20 of 2005)	To provide for the registration and granting of patents for inventions; provides for the patenting of microorganisms and microbiological processes but prohibits the patenting of plants and animals. Amends the Patents Act 57 of 1978 so as to require an applicant for a patent to furnish information relating to the use of indigenous biological resources or traditional knowledge in an invention.	Department of Science and Innovation
Intellectual Property Rights from Publicly Financed Research and Development Act (No. 51 of 2008) & Regulations made in terms of Section 17 of the Act	The Act applies strictly to intellectual property created with public funds. Provisions stipulate that institutions that create intellectual property with public funds will own the intellectual property, regardless of what may have been agreed between the parties. In terms of the Act, the private entity may only become a co-owner of the intellectual property if, inter alia, there is joint creatorship of intellectual property, or appropriate arrangements are made for sharing benefits with the intellectual property creators.	Department of Science and Innovation
Intellectual Property Laws Amendment Act (No. 28 of 2013)	To recognise and afford protection to Indigenous knowledge as a national heritage and asset, and to ensure that Indigenous communities' benefit from such recognition and protection.	Department of Science and Innovation
Protection, Promotion, Development and Management of Indigenous Knowledge Act (No. 6 of 2019)	Provides for the protection, promotion, development and management of Indigenous knowledge and associated communities; access and conditions of access to knowledge of Indigenous communities; facilitation and coordination of Indigenous knowledge-based innovation and the establishment and functions of the National Indigenous Knowledge Systems Office and Advisory Panel on Indigenous knowledge.	Department of Science and Innovation

The Intellectual Property Rights from Publicly Financed Research and Development (IPR-PFRD) Act, No. 51 of 2008, governs all IP developed through research activities that receive any public funding. The primary purpose of the IPR-PFRD Act and its regulations are to ensure that IP outcomes from publicly financed research and development with the potential to create social and/or economic value are protected and commercialised for the benefit of the people of South Africa. Typically, identification of potential IP is assigned to an Office of Technology Transfer, which is established at the institution where public funding has been received. The Office is responsible for assessing the disclosed invention to assess what, if any, forms of IP may arise from the research and development (R&D) described. Intellectual property can take on a number of forms which may be capable of registration in terms of one or other statute (e.g. South African Patents Act or Trade Marks Act) or which may find protection under South African common law (NIPMO 2018). The Act also provides for several preferences specifying eligibility to utilise and exploit the IP generated. Particular preference is granted to non-exclusive licensing, Broad-Based Black Economic Empowerment (BB-BEE) and small enterprises as well as any parties that seek to utilise the IP in ways that provide optimal benefits to the economy and people of South Africa.

Under the Intellectual Property Laws Amendment Act No. 28 of 2013, traditional knowledge can be protected as IP. This Act enables traditional knowledge holders to administer their traditional IP, as well as commercialise it. The protection and promotion of Indigenous knowledge has been further strengthened by the promulgation of the Indigenous Knowledge Act No. 6 of 2019 which sets out the conditions of access to Indigenous knowledge and coordination of Indigenous knowledge-based innovation. These Acts would apply to marine biodiscovery associated with traditional knowledge.

4. KEY FINDINGS

4.1 MARINE BIODISCOVERY REGULATORY CAPACITY



South Africa has a strong ABS regulatory framework to protect indigenous biological resources and realise benefits from its research and commercialisation. However, the framework was designed with a focus on terrestrial macroorganisms and as such challenges have arisen in its application to marine biodiscovery, which is increasingly focused on microorganisms. In addition, because the regulation of marine biodiscovery is a three-step process with multiple institutions responsible for issuing permits, institutional overlaps and confusion have arisen. At times, the stringency of the regulations has led to delays in research programmes and hesitancy by the international scientific community to collaborate with South African researchers. The annual reporting for both discovery and commercialisation is extensive and, although most of the questions are appropriate for the commercial phase, many are premature for the discovery phase. This creates significant administrative burden for both researchers and the DFFE (Jaspars *et al.* 2021).

South African researchers are reportedly complying with permitting regulations, however, given the complexity and fragmentation of the current system the acquisition of the correct permits can be very challenging. This is further complicated by the range of environments from which samples can be collected which do not always have clear cut regulations. Uncertainty about the permitting institution and jurisdiction create further concerns. For example, marine sediments of interest for actinobacteria, are a grey area.

> *"Getting permission to sample the sediments was an experience. The first point would be to look at the Department of Environmental Affairs. When I contacted them they weren't too sure which permit I should apply for because we weren't going to collect any fauna or flora and we were going to collect sediment samples on a small scale. There is a permit for if you want to collect a couple of kilograms to tons, but we were only looking at small samples. They suggested I contact CapeNature. When I contacted them, they said there's nothing they can do about it if it's not going to be in one of their parks. I decided to focus on SANParks locations only because they have a very clear process on their website. That in itself took a very long time because they weren't sure what to do with the biodiscovery aspect, since they don't encourage any bioprospecting on any samples collected within their parks. I also had to get permission from the City of Cape Town because two of the sites were within their borders and they have a process for people who want to do research within the City of Cape Town area"* (Interview 6, SA scientist, 2nd December 2020).

Due to this complexity, where possible researchers try to minimise the number of permits required. "*I deliberately tried to stay within the Western Cape to get around the issue of transporting samples across borders because I know that there are rules and regulations*" (Interview 6, SA scientist, 2nd December 2020).

Another challenging area for scientists concerns biodiscovery research on pre-existing collections. "*We're sitting with big libraries of compounds, extracts etc. that have been collected over the last 25 years. They are huge repositories of a wealth of chemistry. It's very likely that we'll get hit compounds out of that repository. We have collection permits for everything, but we need to backtrack from where we are now and turn those collection permits into discovery notifications*" (Interview 7, SA scientist, 1st December 2020).

Respondents noted that biological samples are for the most part not exported for a combination of reasons including:

i) South African researchers have the expertise and resources necessary for the analysis of the samples in-country;
ii) the acquisition of export permits is challenging and timeous; and
iii) scientists can readily exchange genetic and chemistry data across borders without permits.

However, there are genetic resources or derivatives that may need to be exported, for example, to send to a service provider that can perform tests on the biochemical compounds that are not readily available in South Africa. International collaborations may be hampered by the need to obtain an export permit, which can take a year or more. Exports must be accompanied by an MTA and a benefit-sharing agreement and this administrative burden is placed on the local researchers and technology transfer offices of the research institutions involved (Jaspars *et al.* 2021).

According to the National Advisory Council on Innovation (NACI, n.d.), regulations under NEMBA often stifle the initiation and/or implementation of projects. Given that the costs involved in bringing biodiscovery to economic reality are so great and the timeframes so long, NACI suggests the government should seek to enter partnerships with the private sector and international partners and keep regulations realistic. Respondents stressed the importance of promoting basic research which may not have an immediately obvious economic opportunity but is nonetheless important for scientific knowledge and capacity.

There is a grey area in permitting procedures between research purely for scientific purposes to generate knowledge, and research for commercialisation as the end goal, but which both undertake the same activity. While the scientific community would like a very clear set of instructions from government as to what is required to be compliant, from a legal perspective, scientists are advised do the legwork and go a few steps ahead of what the current regulations provide for. The argument is that doing so creates a reservoir of practice to aid the government in its development of policy and legislation such that scientific practice and knowledge will be factored into the new laws and policies to regulate biodiscovery. Additionally, "*In foreseeing what those prescripts ought to be and putting into place so that should you make an application you can at least be able to portray the extensive levels that you have undertaken to ensure you are compliant with the spirit of South Africa's environmental legislation*" (Interview 3, SA legal researcher, 8th December 2020). In determining the terms and conditions of research agreements with international partners, scientists do seek to be compliant with South Africa's policy and legislation in the event of commercialisation. However, given the complexity and non-linearity of the scientific processes there was uncertainty around the bioprospecting permits.

"It feels like the landscape is rapidly becoming more complicated. The bioprospecting permits are very murky for marine work. It will be interesting to navigate our way through the process while we bounce backwards and forwards with DFFE" (Interview 7, SA scientist, 1st December 2020).

The Marine Spatial Planning Act, No 16. of 2018, was also highlighted as potentially impacting on the regulation of marine biodiscovery in that it may add an additional procedural step as far as the activity is concerned. While ocean spaces haven't yet been designated for specific activities, "*Whatever permitting systems will be provided for under NEMBA, we would now have to take into consideration the designated marine spatial plan of the zone where that activity is going to occur*" (Interview 3, SA legal researcher, 8th December 2020).

It is noteworthy that DFFE's Phakisa Programme, a fast results delivery programme aimed at boosting economic growth and job creation, includes projects on both the Oceans Economy and the Biodiversity Economy yet does not include an explicit focus on marine genetic resources and biodiscovery. This is likely because (a) its social benefits are less obvious than those arising from terrestrial biodiversity, (b) because the resources it targets are, in the case of microbes, "invisible" and largely out of the public and regulatory eyes, and c) for biotrade, are largely within the realm of fisheries management, and for biodiscovery, have not yet seen commercial success.

4.2 MARINE BIODISOCOVERY SCIENTIFIC CAPACITY

"We [South Africa] have very bright people who are doing very interesting research, but right now it's very much pie in the sky type of stuff. Realistically, whether they're actually going to find something, I don't know" (Interview 1, SA scientist, 16th December 2020).

In line with global trends, early biodiscovery in South Africa focused on the discovery of natural products from marine invertebrates and the use of classical chemistry to elucidate the structure of bioactive compounds. However, ensuring sufficient product supply has always been a key challenge.

"Our project has yielded interesting molecules from a chemistry perspective, we've explored the interesting chemistry and a lot of those compounds have been tested, but it really is not going to go anywhere. Quite simply, we can't get enough sponge to extract sufficient quantities of those interesting compounds to do anything in terms of drug discovery. It isn't realistic unless you can find something and synthesise it in the lab" (Interview 1, SA scientist, 16th December 2020).

One approach taken to overcome this challenge is molecular networking which uses sensitive techniques to compare the metabolomic profiles of different species that do not require large samples. The capacity to do the research, including genome and metabolomic analysis, exists in South Africa but infrastructure constraints limit how far down the pipeline scientists can go in-country. For example, while most universities now have genetic sequencing capacity, they lack the vast computing infrastructure required for metabolomics. However, some progress is being made. For example, Rhodes University is partnering with SAIAB to develop a shared server to enable analysis of mass spectronomy data of compounds to create metabolome libraries. Metabolome libraries can be mined for bioactive compounds and once a compound is discovered and the scientist knows what to look for, other genomes can be mined much more efficiently. Without such infrastructural developments South African researchers are dependent on overseas universities for access to their computer laboratories with associated wait times and shared credentials.

"You start going for international collaborations in instances where you need supercomputing and you can't manage on your own. They get their names on the paper and you need to get MoUs in place ahead of time" (Interview 10, SA scientist, 25th November 2020).

South African chemists also face instrumentation and funding constraints which impact their ability to tackle complex chemical structures relatively quickly and to develop synthetic sequences to reproduce the natural products. Chemists thus must be selective with the types of molecules they want to synthesise and consider their capacity to do so.

From a research funding perspective, novel microbiology, molecular biology and gene sequencing are more attractive than the chemistry of producing molecules. Thus, to overcome some of the chemistry constraints there is a strong push to develop a central repository for natural products extracts which local and international researchers can access for screening and molecular networking. In this way, even if there is insufficient material to isolate the chemical compound, the class of molecule responsible for the activity can be identified and then possibly be synthesised to reproduce the activity. This approach is a departure from the chemistry norm where "*people tend to work in isolation*". However, given that the cost of a single collection is R100 000 - R200 000, and may only yield 50 samples, a natural repository approach is a "*more rational way of doing things*" to minimise costs and avoid duplication (Interview 1, SA scientist, 16th December 2020). Similarly, creating a compound repository will enable new discoveries in the future when there is better knowledge, technology and infrastructure to interpret the information but the organisms may not be readily available due to the impacts of climate change and other environmental stressors. A central repository is thus considered by scientists to be a critical need, offering a more efficient and cost-effective way of doing research. Some respondents noted, however, that vast, well-managed and easily accessible repositories of extracts and compounds already exist, such as those housed by the NCI, thus developing a new repository may not be the best use of resources.

Because students are required to show novel chemistry to obtain their degrees, emphasis is typically placed on sources that will produce interesting molecules. Given that the identification of molecules from marine natural products is so challenging, few chemists in South Africa are working on natural products which may negatively impact research capacity in the long term. As one chemist expressed, "*I still find the natural products amazing, but it's really tough*" (Interview 1, SA scientist, 16th December 2020).

Considering the drug development pipeline, South Africa has strong capacity to collect, identify, preserve and archive samples, screen for bioactivity, sequence DNA, predict what type of compounds are there and then isolate those. However, there is a chemistry bottleneck to isolate the molecule and solve and confirm its structure. A challenge is to produce it in sufficient quantities to start the drug development process, which is very expensive and requires specialised expertise and infrastructure in cloning and recombinant expressions.

> *"I'd say the potential is there, but we still have a lot of capacity building to do, as well as building the network to get more people in touch who have different complementary skills"* (Interview 6, SA scientist, 2nd December 2020).

4.3 TRACEABILITY OF MARINE GENETIC RESOURCES AND DIGITAL SEQUENCE INFORMATION

Given the expense and difficulty of obtaining biological samples and the limited supply of natural products from these samples, there has been a surge in the use of "omics" technologies to elucidate the genes and pathways responsible for producing bioactive compounds. The result is a mass of digital DSI that is increasingly difficult to trace from origin to end-product, particularly in the commercialisation phase. This is due to the non-linearity of how DSI is used with multiple sequences often combined in the creation of an end-product. While access to physical samples can be controlled, once DSI is in a public database it is readily available, accessible and easily replicated making traceability difficult (Jaspars *et al.* 2021).

Rabone *et al.* (2019) highlight the importance of the use of data standards as key to making data FAIR: Findable, Accessible, Interoperable and Reusable, to simplify downstream applications and allow comparison of data across studies. It is critical that the data stay associated with the contextual information that describes all aspects of the marine genetic resource it was derived from as without the integration of sequence and associated data for a marine genetic resource, the sequence data is of minimal scientific use, as it cannot be placed in its context. Depending on the sample type, these data can include the current taxonomy/identification of the sample, its physical location and preservation method (including preservation history); occurrence and sampling data (where, when and how the sample was collected), associated environmental data (e.g., oceanographic data); and derived sample information (e.g., extractions isolated from a parent sample). In South Africa, good practices within the scientific community are increasingly ensuring traceability of data back to the original marine genetic resources, with local identifiers used by researchers for materials and data derived from resources for biodiscovery. Data are typically maintained in different, locally-based databases linked to particular institutions or projects. Such information may include the location of sample collection, taxonomic identification, links to DNA sequences, biological assay data and biochemical compounds obtained. This level of traceability is not required by law but enables researchers to accurately identify materials of interest for further investigation.

Samples and compounds are often exchanged within local research partnerships through MTAs that detail what research will be undertaken. Within international research partnerships, biological samples are not readily exported due to concerns related to third party use and traceability. "*I'm not comfortable with sharing live biology because it's very hard to track what happens to live material…at this stage I haven't sent any biological material anywhere*" (Interview 7, SA scientist, 1st December 2020). However, interesting compounds may be exported for further investigation where the technology and/or expertise is not available in South Africa with an agreement detailing the materials to be investigated by other partners in the consortium. In contrast to biological samples, genetic and chemistry data are often exchanged through access to a common internal database with MTAs that formally set out the terms and conditions of use.

"We cover any transfer of information and technology through a Material Transfer Agreement that says, 'That's what you're going to do with the information and then we're going to share the results'. In terms of chemistry, if there are any compounds exchanged between researchers it's also covered by an MTA that very specifically covers what the receiving institution is going to do with those materials" (Interview 7, SA scientist, 1st December 2020).

"What we're trying to do in the South Africa Hub is to make sure that there's a well-structured database for any samples coming in where all the relevant metadata is collected and stored so that we've got a very detailed history of every isolate or compound coming in - what they've been used for before, who generated them, who isolated the bacteria, what animal it came from, what region" (Interview 12, UK scientist, 3rd March 2021).

While the export of materials is covered under NEMBA and requires a Biodiscovery Export Permit, DSI is currently not regulated in South Africa. The question of whether DSI should be covered by NEMBA and subject to benefit-sharing provisions is under active discussion within the South African Government.

"We aren't exporting any live material. We get into the interesting area of exchanging information, which will be data from genetics and metabolomics. I don't know where that lies. I don't know if it is included in NEMBA. Those are things we're going to need to think about" (Interview 7, SA scientist, 1st December 2020).

The issue of DSI was raised as a legal blind spot in relation to the onsite sequencing of genetic data during sampling expeditions.

"That's a game changer. I can tell you now, the lawyers haven't considered the implications of that and how we even regulate that. This is the case in any public sphere. The technology and science is always way ahead" (Interview 3, SA legal researcher, 8th December 2020).

Drug discovery and development is slow, and it takes several years to generate the data to support a patent application if an interesting compound is found. Scientists highlighted the need to apply caution in sharing any data related to analysis until patents are in place and/or data has been sufficiently analysed. Thus, while data may be loaded onto a public database with an embargo until it is ready for publication, in most cases the data are withheld within the partnership and only shared on internal databases until there is IP in place. On average the data will be made publicly accessible within five years.

"We have published some of the genomes and for others, we're holding onto them because of patenting reasons later down the line. We hold onto an organism's data if we think we have something hot and exciting" (Interview 9, SA scientist, 26th November 2020).

Following patenting and publication or sufficient investigation without success, data are uploaded onto public databases together with metadata specifying the origin of the data and how they were obtained. Most genetic data are currently uploaded onto the main databases (e.g. GenBank, NCBI) however the value of a database specifically for marine data was highlighted.

"It would be great if there was a centralised place where, for example, all marine-related data can be stored. At the moment you have to filter through a lot of databases to try to find related marine data" (Interview 6, SA scientist, 2nd December 2020).

Once public, the subsequent use of information for the development of compounds in pharmaceutical companies is challenging to trace as there is no clear way to discover it in the patent literature due to structures and associated compound names or codes changing.

"I think it's critical that the data needs to be protected or that there's ownership of that data because if a big company, like Pfizer or AstraZeneca or whoever, mines that data and they find a pathway that gives them an idea to develop a new antimicrobial compound it's difficult to track where that idea came from" (Interview 7, SA scientist, 1st December 2020).

With local awareness of "fair game" and no obligations to the country of origin from innovations derived from data in public databases, scientists would like data to be protected in some way but recognised the difficulty in implementation. Centralised databases with access agreements were suggested as one way of generating benefits from innovations.

"Once it's out in the public domain there's nothing much you can do about it, whereas some form of gatekeeping could be put in place if you have a centralised hub. If someone wants to access the data, they have to sign an agreement to indicate that if something were to come from that information then the initial source will be protected or considered" (Interview 6, SA scientist, 2nd December 2020).

"Unless you have a repository and people apply to get specific datasets and then you've got to sign what you're going to use that data for, as well as sign to return revenue back to the country of origin if something is commercialised" (Interview 10, SA scientist, 25th November 2020).

Among researchers there is concern that some sensitive data may have already been inadvertently shared without sufficient protections in place.

"I think a lot of things have probably slipped through that we're completely unaware of. We're starting to wise up, but we're far behind the curve in this area. That's why we need people to educate us because we're very trusting and leave ourselves wide open to exploitation" (Interview 10, SA scientist, 25th November 2020).

Unlike genetic data, chemistry data are not commonly kept in public repositories but there is recent interest to create chemical repositories to help avoid duplication and maximise resources. For example, the University of California San Diego has created the Global Natural Products Social Molecular Networking repository for the open access sharing of mass spectrometry data. However, creating chemical repositories is far more complex as every natural product has unique chemistry, whereas for molecular biology the scope is limited to the four nitrogenous bases in DNA. The power of repositories is that new data are constantly being added, enabling more efficient analysis and possibilities for reanalysis as more information is added.

4.4 INTELLECTUAL PROPERTY

While the Patents Amendment Act requires disclosure and proof of permission for the use of an indigenous biological resource, genetic resource, or traditional knowledge it was highlighted that "*South Africa is a non-examining authority and that's a very big problem. They'll grant you the patent as long as your documentation is in order*" (Interview 4, SA legal researcher, 3rd December 2020). Therefore, the issuing of patents requires external vigilance regarding what patents are being granted, particularly where genetic material is involved. Moreover, most patents of commercial interest will be filed in countries where disclosure requirements do not exist.

According to the scientific community the law concerning IP is clear. "*We're publicly funded and therefore the IP belongs to the public. The university owns the intellectual property and has the responsibility of protecting that".* However, as one scientist remarked, *"it gets tricky when you're looking to sell to a commercial company that's not public*" (Interview 7, SA scientist, 1st December 2020). One option is for research to be co-funded, for example as part of an international research partnership. Where research is co-funded, a funder may also become a co-owner of IP from publicly financed R&D provided that all of the following conditions have been met: (1) there is benefit sharing to reward IP creators; (2) there is joint creation of IP; (3) there is an agreement to commercialise the IP; and (4) there is a contribution of resources by the funder (which can include background IP, in-kind contributions, etc.).

Research and development conducted at Full Cost do not fall within the scope of the Act. Full Cost is where all direct and indirect costs attributable to conducting the research are charged to the funder. In this case a funder can negotiate with the university to wholly own the IP generated and the university is required to declare the Full Cost Model in use to the National Intellectual Property Management Office (NIPMO) who reviews and approves the model. In terms of any resulting IP, while each agreement is unique, generally industry standards apply whereby IP is determined by intellectual input.

> *"If you're active in this area you should have reasonable expectations around what constitutes intellectual input and how you measure the amount of effort that's gone into the development of something. The earlier those agreements are put in place and the earlier those discussions are had the better"* (Interview 12, UK Scientist, 3rd March 2021).

However, it was acknowledged that it can be difficult to discern exactly who contributed to the inventions and should be on the patent versus who would be considered to have assisted that invention to be possible, as well as what contribution that would be in relative merit and percentage. In many cases the complexities mean it can be difficult to reach a resolution.

4.5 CONVENTION ON THE LAW OF THE SEA (UNCLOS)

4.5.1 Legal blind spots

UNCLOS recognises the sovereign rights of states over their marine biodiversity and sets out provisions for countries to govern their areas of national jurisdiction. These include provisions relating to access, protection and preservation of the marine environment and exploitation of living and non-living resources, amongst others. In addition to sovereign rights to the EEZ and continental shelf, states can apply to extend their continental shelf by 150 nautical miles affording sovereign rights to the mineral and other non-living resources of the sea that are in the subsoil, together with living organisms belonging to sedentary species. When considering sovereign rights to the sedentary species occurring on an extended continental shelf under UNCLOS, disputes can arise between countries over whether to classify certain species as sedentary or not impacting regulatory obligations under the Marine Living Resources Act and NEMBA. For example, hydrothermal vents and their associated organisms located on an extended continental shelf could be disputed as being sedentary as, "*those organisms can't* *survive without constant contact with the vent, which originates from the seabed*" (Interview 4, SA legal researcher, 3rd December 2020). Any users of these associated organisms would be required to comply with the Marine Living Resource Act, NEMBA and BABS Regulations. Further the concept of "at a harvestable stage" in the definition of sedentary species is up for interpretation as it relates to marine biodiscovery where DNA is being sampled rather than an organism at a particular life stage.

Another key issue raised is that under Article 244 of UNCLOS, "*States and competent international organizations shall, in accordance with this Convention, make available by publication and dissemination through appropriate channels information on proposed major programmes and their objectives as well as knowledge resulting from marine scientific research*". Therefore, if South Africa grants permission for marine biodiscovery research to be undertaken in its EEZ, the government is obliged to publicly disseminate information pertaining to the nature and objectives of the project and any knowledge generated. This creates a challenging nexus between the private and public elements of the law which may create areas of contention and may serve as a deterrent for entities that have the financial resources to undertake such activities but may not necessarily enjoy the commercial gain from those activities.

"For anyone who wants to undertake an activity in light of this project for commercial gain, it's going to be particularly challenging because there is then no perceived commercial value considering that you have to disseminate all the information/knowledge that you garner. That affects IP" (Interview 3, SA legal researcher, 8th December 2020).

Legal experts have suggested that there needs to be some sort of interpretation of what is meant by the "dissemination of knowledge" and what is the breadth of South Africa's obligation with regards to activities undertaken in its ocean spaces and the extent to which the state or least developed countries will benefit from such research. For example, clarification is needed regarding whether it would be sufficient for just the genetic data to be published or whether there is an obligation as far as intellectual property is concerned. Currently, there is a developing policy framework and states are trying to navigate this contentious issue by balancing political objectives and commercial demand.

On a regional scale, marine biodiscovery is difficult to regulate as organisms are not bound by geopolitical boundaries, yet the delimitation of maritime boundaries is politically rather than ecologically motivated. "*From a scientific point of view, there's a lot of conflict when it comes to the zonal demarcations as ecosystems and organisms don't prescribe to boundaries*" (Interview 4, SA legal researcher, 3rd December 2020). South Africa's maritime boundaries with both Namibia and Mozambique are not yet delimited. Further, neighbouring countries have varying capacities to develop and implement regulatory frameworks. This in turn may influence where research is undertaken as the severity of the law will determine the accessibility of the resource.

4.6 BENEFIT SHARING

South Africa's immense diversity of marine genetic resources offers an opportunity for a range of benefits to be accrued to the country through the negotiation of benefit-sharing agreements for access to biodiversity. However, given the absence of commercial products, benefit sharing for biodiscovery in South Africa has largely centred on the development of scientific research partnerships. This has yielded important benefits for the South African research community, including the training of postgraduate students, access to external repositories, the development of local repositories, joint publications, knowledge sharing, technology transfer, long-term collaborations and developing critical mass in fields such as microbiology. Increased accessibility to marine genetic resources and associated benefits can enable improved outcomes for biodiversity conservation through the sharing of resources to generate inventories of taxonomic and distribution data important for monitoring and marine spatial planning, support for fundamental biodiversity research, collaboration between research institutions and government conservation agencies, and the sharing of genomic data.

4.6.1 Repositories and databases

In the 1980s when the NCI was undertaking extensive collections of plant samples from around the world, the issue of benefit sharing was raised. This led to the subsequent development of a Letter of Collection which provided a framework for the NCI to enter into an agreement with a provider country, as the CBD had yet to come into existence. The Letter of Collection and Collaboration Agreement are used by the NCI to enter research partnerships with benefit-sharing agreements and have formed the basis of many other agreements (Cragg *et al.* 2012).

"Once the NCI got involved, it's interesting that this raised the issue of benefit sharing to a new level. The NCI is by far the biggest research programme in looking for drugs from nature. This raised global interest worldwide" (Interview 11, NCI, 24th February 2021).

As part of the NCI's natural products program three repositories have been developed from the samples collected worldwide and are available for scientists to access. The Open Repository Program, initiated in 1992, offers external research organisations access to natural products which have not met the current requirements of the cancer screens, to investigate as potential sources of agents for the treatment of all human diseases.

"They're available to scientists worldwide to test for sources of interesting new drugs for whichever human disease they're studying. They have to sign a Material Transfer Agreement in order to access the extracts, which effectively spells out the same issues as the Letter of Collection for protecting source countries. If any discovery is made from that, the investigators have to go back to the source country and establish agreements" (Interview 11, NCI, 24th February 2021).

The Active Repository Program enables qualified researchers from the U.S. to investigate materials that, since January 1996, have been judged to be active in a 60-cell line anti-tumour screen. A publicly accessible prefractionated library of extracts and fractions is also available for high throughput screening free of charge.

In addition to accessing external repositories is the opportunity for benefit-sharing agreements to contribute to the development of national repositories, including biobanks and databases. A positive outcome of the ABS legislation is the creation of the National Biobanks Initiative, funded by Germany, which will curate collections of South African species, including marine species, and make the database searchable globally via GBIF (Jaspars *et al.* 2021). Not only do local repositories prevent duplicates in sample collection and extracts, but they also provide baseline data for taxonomic and distribution data essential to biodiversity conservation and environmental monitoring.

4.6.2 Partnerships, capacity building and technology transfer

Explicit monetary and non-monetary benefits are typically the negotiating focus of benefit-sharing agreements. However, benefit sharing is often iterative and more subtle and in the form of an ongoing partnership between two researchers with mutual interests who put an agreement in place between their respective institutions. "*We have frequent phone calls about things he might want to develop or do and I find opportunities that he might want to work with and we publish papers together*". Added to this is mentoring for both parties and the sharing of local knowledge, *"I give advice on how to structure a grant for the UK funding agency, but he gives me advice on what's relevant to local society and economy*" (Interview 13, 19th February 2021). These partnerships result in long-term collaborations that span decades and enable support for the development of research capacity, facilitate funding, spark innovation and strengthen transparency and reciprocity in the scientific community.

Often, new collaborations are forged because of existing partnerships. For example, Rhodes University has been involved in the African Coelacanth Ecosystem Project (ACEP) which is predominantly a taxonomic project of the South African National Biodiversity Institute (SANBI) to document species and their distribution along the east coast from Tanzania to South Africa. However, through the ACEP new collaborations have been forged between Rhodes University and researchers in Kenya and Tanzania developing their own marine biodiscovery project with the intention to establish networks and support them in strengthening research capacity in those countries.

Another component of benefit sharing is capacity building and technology transfer. For example, the NCI invites any collaborating group to its labs for training in screening, fractionation, and drug discovery chemistry at the NCI's expense. Such exchanges were crucial to the development of South Africa's research capacity in the early years and more recently partnerships such as those between PharmaSea and the University of the Western Cape have been instrumental in developing critical mass in microbiology. Chemists have highlighted the need for comprehensive chemical extract libraries and additional infrastructure and instrumentation to advance capability in the isolating and optimisation of interesting compounds which international research collaborations may enable.

4.6.3 Fundamental research and neglected pathogens

Taxonomy underpins scientific understanding of biodiversity yet with increased focus on technology, capacity in taxonomic research is waning. The importance of channelling funding for taxonomy/biodiversity research was highlighted, together with the harnessing of international funds for neglected pathogens or those most relevant to South Africa. For example, in Ghana the UK Medical Research Council is funding research on parasites specific to the country while the Leverhulme Trust Fund specifies funds to be used for something that is locally relevant.

4.6.4 Biodiversity conservation

Traditionally marine biodiscovery was considered a potential threat to marine biodiversity as it required much larger samples of marine organisms to isolate the secondary metabolites and conservation of the species was not always considered by early scientists.

> *"Supply is one of the hazards of natural drug discovery. It has been a threat to conservation, particularly in the old days where someone would go out and collect a couple of tons of the source organism"* (Interview 11, NCI, 24th February 2021).

For example, to produce a gram of dolastatin 10, one of the most promising anticancer compounds discovered in the 1960s, a ton of the Mauritian sea hare *Dollabella auricularia* was harvested. Today, technology enables onsite genome sequencing or for much smaller sampling at higher resolution. Further, while early marine biodiscovery was hampered by obtaining a sustainable supply of the metabolites, now technology is used for the synthetic production of the compound in host organisms.

> *"In terms of sustainability, we don't need the original samples anymore once we've got a bacteria colony growing on a plate in a lab. That's a much more sustainable way of accessing any bioactive molecules"* (Interview 12, UK scientist, 3rd March 2021).

> *"Microbes are exciting because you can grow them in tanks if you find something, whereas you don't have to wipe out a poor tunicate or medicinal plants"* (Interview 11, NCI, 24th February 2021).

Marine biodiscovery thus poses far less of a threat to species than it did historically and other environmental stressors and economic activities such as mining, fishing and pollution put marine biodiversity more at risk. However, the advent of technology has brought new conservation risks such as those associated with seabed mining.

> *"I think, personally, the risk is more in terms of biodiversity and the loss of these organisms and not being able to access them with climate change and everything"* (Interview 1, SA scientist, 16th December 2020).

As a signatory to the CBD and UNCLOS, "*South Africa has the right to explore and exploit living and non-living resources in areas under national jurisdiction, but it is also coupled with the duty to protect and preserve the natural biodiversity from the activities that are undertaken over there*" (Interview 3, SA legal researcher, 8th December 2020). However South Africa is challenged by fractured governance in the marine sphere which is not necessarily aligned with other aspects of biodiversity and conservation.

Biodiversity conservation is considered to be critical by South African scientists as, "*We have truly South African molecules that are only produced by organisms in South Africa*" (Interview 1, SA scientist, 16th December 2020). Therefore, the future potential of marine biodiscovery is itself motivation for conservation of the marine environment. "*If we can make use of the data we generate to highlight how actions along the coastline can impact the microbial biodiversity, then we can use it as an indicator that certain areas must be protected*" (Interview 6, SA scientist, 2nd December 2020). Currently extensive foundational marine biodiversity data such as distribution records, genetic barcoding, and red list assessments are being collected by SANBI including the African Coelacanth Ecosystem Programme, Sea Keys and Sea Map, with the latter having a strong molecular component particularly for marine invertebrates. Communicating the benefits of marine biodiscovery is an important strategy to motivate for the establishment of marine protected areas, marine spatial planning and a more holistic approach to the ocean economy. "*For me, it was a critical argument when I stood in front of Cabinet motivating for these new protected areas*" (Interview 5, SA conservationist, 2nd December 2020).

Partnerships between government agencies such as SANBI and research institutions offer an opportunity for conservation benefits to be enhanced. Similarly, conservation measures can be incorporated into research and benefit-sharing agreements. For example, research funding can be made available for boats and equipment or resources shared for sampling expeditions to generate inventories of taxonomic and distribution data important for monitoring and marine spatial planning. Box 5 provides further examples of non-monetary benefits for biodiversity conservation from biodiscovery research.

BOX 5: Examples of non-monetary benefits from biodiscovery research that support conservation of marine biodiversity

- Research collaborations that bring together specialised expertise, resources and infrastructure.
- Scientific and environmental education and training with institutions undertaking biodiversity and conservation research, conservation authorities, traditional knowledge holders and resource custodians.
- Capacity building that can be applied to fundamental biodiversity research including taxonomy and phylogenetics through knowledge exchange and training.
- Capacity building in specialised expertise, equipment and infrastructure that may not be available in South Africa but has application to biodiversity research and conservation with a focus on biodiversity institutions such as SANBI, SAEON and other relevant research institutions.
- Acquisition of specialised equipment and infrastructure that may not be readily available with a focus on deep-sea sampling.
- Support for biodiversity and conservation research in funding proposals.
- Sharing data and information in national and/or public databases with accurate metadata for ease of access to avoid duplication of research and enable interoperability.
- Alignment of research programmes to conservation priorities of the area and/or national priorities.
- Research feedback to conservation authorities and partnerships between government agencies such as SANParks and research institutions.
- Sharing data and information with conservation authorities about resources that are accessed to inform resource management decision making.
- Depositing samples in repositories including biobanks, genebanks, chemical extract libraries and museums that contribute to the conservation of threatened and rare species and for use in other research.
- Access to and transfer of technology related to the marine resource or applicable to biodiversity research and conservation, for example, omics technologies that can be used to generate genetic data for taxonomy or analytical technologies for molecular networking of species to investigate environmental factors.
- Including conservation benefits in collection permits and benefit-sharing agreements.

Deep-sea sampling is an important component of biodiversity research for conservation, however the associated costs are prohibitive. "*You have to understand the inequity in deep sea research…We're lagging so far behind in deep sea research because it's expensive to get out there and once you're out there it's expensive to get your expensive toys down on the seabed*" (Interview 8, SA conservationist, 26th November 2020). Therefore, a key challenge for South Africa is to leverage international support for deep-sea research as, "*One of our obstacles is that we don't have academic leadership in deep sea research to take that forward. It's really difficult because it's so expensive*" (Interview 5, SA conservationist, 2nd December 2020).

Another way in which marine biodiscovery can contribute to conservation is through the sharing of DSI. While researchers at academic institutions may be focused on sequencing data targeted towards marine biodiscovery, sequencing data can contribute to the development of eDNA databases for environmental monitoring to assist with biodiversity management and marine spatial planning. Within government, molecular research for conservation is least developed and poorly coordinated, thus there is an opportunity to imbed data sharing requirements for conservation within marine biodiscovery research.

4.7 INDIGENOUS AND LOCAL KNOWLEDGE IN MARINE BIODISCOVERY

The vast nature of the ocean and the fraught history of colonisation and apartheid means that the links between Indigenous and local knowledge (ILK) and marine biodiscovery activities in South Africa are poorly understood. Thornton and Scheer (2012) estimate that only 2-8% of published articles on marine ILK are from the African continent. Within southern Africa, research that focuses on marine ILK pales in comparison to the epistemological links established between ILK and terrestrial biological diversity and there is limited research on the connections that ILK-holders share with the ocean and on ILK associated with the use of marine biodiversity. However, the lack of research into the connections between ILK and marine biodiversity in southern Africa does not imply an absence of knowledge. Due to the ongoing inaccessibility of much of the ocean and its biodiversity to coastal communities and ILK-holders (Armitage *et al.* 2020), scientists with financial and technological resources are much more able to explore, use, and come to know (scientifically) the ocean and its resources. Considering this, the connections that ILK-holders share with marine biodiversity may be disrupted and/or less direct than the connections they share with terrestrial biological resources.

The systematic search and scientific collection and classification of marine taxa in South Africa has been ongoing since the colonial period with subsequent modern marine biodiscovery developing alongside technological advancement (Griffiths *et al.* 2010). The discovery and use of marine biodiversity by local communities however, is an ancient practice in South Africa and throughout the world. Shell middens found along South Africa's coastline demonstrate a wealth of paleontological evidence that show how coastal people were actively foraging marine resources like mussels, barnacles, whelks, limpets, tortoises, fish, and birds from 3000 BP (McGrath *et al.* 2015). Much of this archeological research pertains to the caloric potential of intertidal resources that sustained and physiologically developed coastal populations, rather than their non-food uses. Research undertaken in the humanities/medical anthropology may be an alternative source for understanding the potential role of foraged marine resources outside of their use as food and sustenance and points to the need for transdisciplinary engagement on the potential connections between ILK and marine biodiscovery (Stewart *et al.* 2015). Further, opportunities exist for meaningful collaboration between scientific and Indigenous knowledge systems.

Historical documentation of traditional knowledge associated with the use of marine invertebrates dates back to ancient times. Multiple examples can be found in Indian, Chinese, Greek, and Arabic materia medica, and refer in particular to poriferans, coelenterates, echinoderms, molluscs, and crustaceans (Voultsiadou and Vafidis 2007; Gopal *et al.* 2008).

The earliest example of successful industrial use of a marine-origin natural product is perhaps the highly-valued dye, "tyrian purple", extracted from molluscs and traded by the Phoenicians from 1600 BC (Whittle 2009). Seaweeds (or marine macroalgae) are another group of marine organisms that have a long history of use in food, industrial, agricultural, and cosmetic applications amongst coastal communities throughout the world (Mouritsen *et al.* 2021) and continue to be of interest to both coastal people and industry. Traditional uses of marine biodiversity and associated knowledge do not only lie in ancient history but continue to thrive and evolve today. A study by Herbert *et al.* (2003) surveyed invertebrates on sale at the Warwick Triangle traditional medicine market in Durban, noting a prevalence of poriferans, cnidarians, molluscs, echinoderms, and chordates. A similar study by Whiting *et al.* (2013) that surveyed the Faraday market in Johannesburg also noted the presence of marine organisms but to a lesser extent - most likely due to its urban - rather than coastal location. It is noteworthy that many of the marine species observed by Herbert *et al.* (2003) belong to groups that have proven to be rich in bioactive natural products, namely sponges, cnidarians, molluscs, echinoderms and tunicates, pointing to the potential of marine traditional knowledge as a source for novel bioactive compounds.

These localised studies show that there are ongoing ocean connections and interactions in both coastal and urban areas that researchers do not yet fully understand. This also points to the potential incompatibility of traditional knowledge and scientific ways of knowing marine biodiversity in relation to marine biodiscovery. Traditional knowledge systems comprise not only of medicinal-use knowledge that can, in some instances be translated into the scientific knowledge framework, but there are also spiritual dimensions of knowledge associated with plants and animals that cannot be readily translated into scientifically evaluated and medically approved patent medicines (Williams and Whiting 2016). Any potential collaborations between traditional knowledge holders and scientists involved in marine biodiscovery would need to ensure that desirable elements of traditional knowledge associated with marine biodiversity were not taken out of context. In other words, it is imperative that scientists, or anyone working with traditional knowledge holders refrain from a purely utilitarian consumption of traditional knowledge that extracts knowledge that might be termed "useful" to the project objectives but rather respects the full integrity of traditional knowledge as a living body of knowledge that transcends social, ecological, political, economic, and spiritual boundaries. The live, evolving, and holistic nature of traditional knowledge lends itself well to interdisciplinary and transdisciplinary engagement that draws on multiple bodies of knowledge.

5. RECOMMENDATIONS

South Africa's status as one of the most biologically diverse countries in the world offers the country exceptional opportunities to significantly benefit from research and innovation in marine biodiscovery. Although several candidate species have shown potential, there has yet to be a successful commercial product arising from the use of South African marine genetic resources. Harnessing the potential of South Africa's marine biodiversity can help address economic and societal challenges and support biodiversity conservation. However, to do so requires the development of specialised expertise and infrastructure for the whole biodiscovery pipeline through enhanced coordination of research and the deployment of funding and resources in focused areas. While significant research capacity exists in-country and multiple biodiscovery research programmes are underway, most research is undertaken through universities with limited access to funding. Thus, enabling opportunities for commercialisation also requires identifying, harnessing and creating linkages between scientific knowledge, national priorities and market opportunities.

Effective governance of marine genetic resources is critical to stimulating research and innovation and ensuring equitable benefit sharing. Regulations pertaining to access to marine resources and the use of DSI require careful consideration to avoid burdensome bureaucratic processes that disincentivise research. A light-touch governance approach focused on streamlined permitting processes and aligning these with scientific best-practice in data management and traceability should be employed.

Specific actions that can be taken by government towards enhancing South Africa's marine biodiscovery capability include:

Steps towards effective governance

- Clarify and streamline permitting processes with a focus on the provision of clear institutional guidelines from each agency specific to marine biodiscovery. These guidelines should be readily available online in a "one-stop-shop" with links to the relevant forms and submission contact details.
- Give attention to the way in which permitting occurs for microorganisms and for different kinds of marine environments and ecosystems.
- Develop a policy for the way in which DSI is regulated and managed and link to a broader policy for DSI, ABS and scientific research in South Africa.

Steps towards enhanced research capability and commercialisation

- Facilitate and support local and international research partnerships.
- Promote collaboration between scientists and the coordination of projects.
- Maximise the use of existing research infrastructure and enable access to other essential infrastructure available.
- Initiate a marine biodiscovery pipeline analysis to identify the strengths and gaps towards a strategy for developing South Africa's capability for commercialisation.
- Direct resources towards gaps in the biodiscovery pipeline, most notably chemical analysis, optimisation of compounds and pre-clinical development of products.

- Encourage and support partnerships between researchers and industry.
- Create a national marine biodiscovery resource centre with strong connections to other relevant national and international research centres to help eliminate bottle-necks in the discovery pipeline.
- Create as a component of the resource centre, a marine biobank/repository with appropriate data management systems to ensure that data relating to species, samples, processing and the distribution of samples are developed and maintained to industry standards.

Steps towards societal and environmental benefits

- Leverage benefit-sharing agreements and partnerships to support the development of national biobanks and databases, fundamental biodiversity research, and training, capacity building and technology transfer for marine biodiscovery.
- Ensure that marine conservation is explicitly supported in the development of biodiscovery research agreements, partnerships and commercialisation arrangements.
- Engage a range of societal actors including academia, citizens, industry, and others in research and innovation to better align biodiscovery and its outcomes with the values, needs and expectations of society.
- Give priority to supporting research that targets local environmental and social needs.

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