7 The race for the oceans' genetic diversity

> In the course of evolution, marine life has developed an astonishing variety of ingenious forms, functions and survival strategies. Marine-derived natural products and pharmaceuticals may therefore deliver progress and profit in many different economic sectors. However, it is still largely unclear who exactly may profit from the oceans' genetic diversity, how it can be used fairly and, above all, how its conservation can be guaranteed in the long term.

Marine-derived active compounds

> The expectations are huge: since the first successes of marine biodiscovery research, scientists have been hoping to find solutions to humankind's most pressing problems in the genome of marine organisms – from pharmaceuticals to treat previously fatal diseases to cosmetics for eternally young skin to formulas for environmentally friendly adhesives and paints. However, to decode genetic information is still a complex undertaking, even if modern high-throughput methods have enormously accelerated the process.

Unparalleled diversity

Marine life is unique and exceeds terrestrial species diversity many times over. In part, this diversity is owed to the fact that life on Earth first evolved 3.7 billion years ago in the oceans and only subsequently conquered the land. In retrospect, marine life had about three times more time to conquer the many niches of the ocean and adapt to the prevailing environmental conditions than land-based plants and animals. At the same time, marine organisms were forced from the outset to adapt to particularly extreme habitats. Deep-sea dwellers, for example, have to cope with the enormous pressure exerted by the water column, constantly low temperatures, little food and constant darkness. If they also live at one of the many hydrothermal vents, extreme chemical stresses are added – for example, a carbon dioxide content that can exceed by a factor of 1000 the concentration in the air we breathe.

Quorum Sensing
"Quorum" sensing is the term used to describe a bacterial cell-to-cell signalling process that is dependent on cell densities and only takes effect when the concentration of certain signalling molecules emitted by the bacteria exceeds a certain threshold value in the medium.

Challenged in this way, marine life has developed a wide range of ingenious forms, functions and strategies in the course of evolution and encoded the information for the formation of these characteristics in the marine organisms' genetic material. There are an estimated 2.2 million different species of marine animals, plants and fungi today, and about 230,000 of them have been scientifically described. The number of bacterial, archaeal and viral species is unknown. But it is known that, measured by their weight, they make up the bulk of life in the ocean. One drop of seawater can contain up to 350,000 different species of bacteria and other microorganisms.

The genetic diversity of marine animals, plants and various microorganisms is the foundation of life in the ocean. It influences, for example, how much biomass marine biocoenoses produce, to what extent they reproduce and how resistant they are to stressors. Species with high genetic diversity have greater fitness, adapt more quickly to environmental change and recover faster on foot of an environmentally induced population collapse. The ocean's gene pool thus helps determine how much food and other services the sea can provide to humans in the long term.

For scientists, the oceanic genome, i.e. the genetic resources present in all marine biodiversity as well as the many pieces of information they store, is akin to a gigantic library. Here they search for information on the development of marine organisms and their ability to adapt to their respective habitat and the changes therein. But also encoded in the genome are the blueprints for what are known as secondary metabolites, which are of particular interest to chemists and molecular biologists. In contrast to primary metabolites (e.g. nucleotides, amino acids), which serve to build vital biomolecules (e.g. DNA, proteins), secondary metabolites are not considered essential for the survival of the organism that produces them. They can however fulfil important ecological functions.

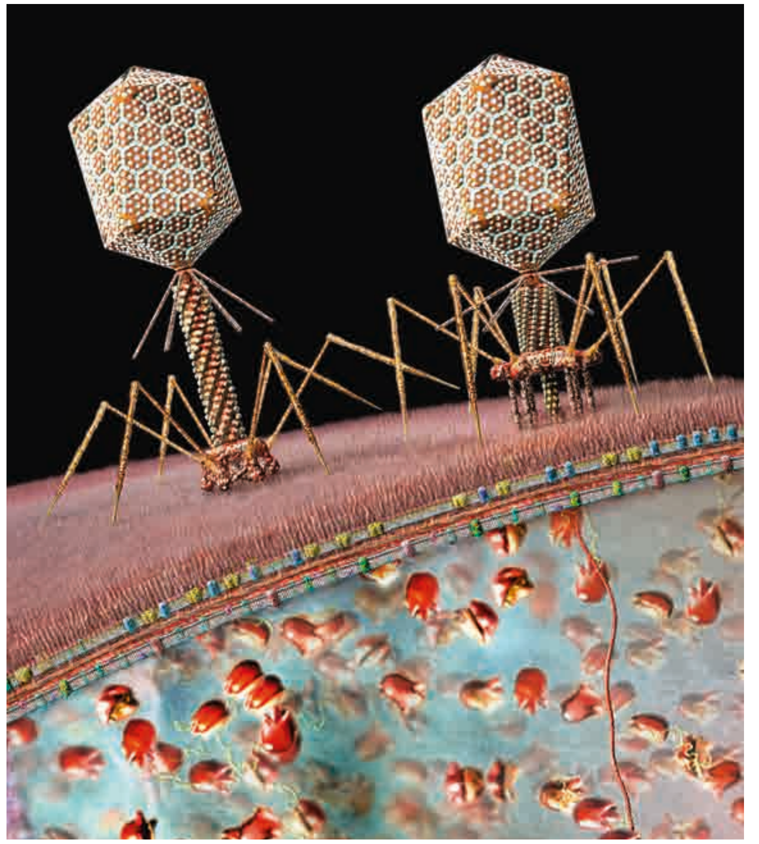
Secondary metabolites are produced by marine animals, plants, fungi, bacteria, archaea and viruses for various purposes. They serve, for example, as a chemical weapon for catching prey (as in the marine cone snail of the genus *Conus*), and also aid communication between organisms by means of chemical signals (quorum sensing in bacteria) or protect against extreme temperatures, UV radiation, pathogens, fouling, intrusive neighbours or predators. Secondary metabolites therefore noticeably improve the performance and adaptability and thus the chances of survival of marine organisms and are generally – and this is what is so special about them – enormously effective even in very small quantities.

For a little over two decades, marine scientists working in the field of marine natural products chemistry and the closely linked field of marine biotechnology have been actively researching marine secondary metabolites and their use by humans in the form of marine-derived active compounds. The scientists involved in this field examine marine organisms for the presence of bioactive, i.e. effective, molecules and components, extract them, describe their chemical structure, explore their function and look for possible commercial uses – ranging from the feed and food industries to the production of cosmetics and pharmaceuticals.

In addition to molecular research, biotechnologists investigate the extent to which fish waste, marine algae and microorganisms could be used as natural products for industrial purposes. German scientists, for example, are currently investigating whether edible food packaging can be produced from macroalgae. These could replace plastic packaging and disposable tableware and could also be enriched with bioactive ingredients that prolong the foods' shelf-life. Collagen can be extracted from fish scraps and used in a variety of ways – as a food supplement, as an agent to help repair tissue damage, as an additive in cosmetics production and as an agent against the formation of biofilms on surfaces. Scientists even suspect the presence of valuable active compounds in the ink of octopuses and cuttlefish.

The potential range of applications for marine-derived active compounds is so vast that experts are looking to the ocean for solutions to some of humankind's greatest problems. These include, among others:

- combating previously incurable diseases by developing new pharmaceutical compounds based on marine-derived active compounds;
- improved preventive healthcare by adding marine-derived active compounds to food products in order to make them more nutritious, vitamin-rich or digestible;
- development of biodegradable substitutes for plastics and other petroleum-based materials;
- development of environmentally friendly anti-fouling paints, adhesives and biofilters modelled on marine microorganisms;
- development of new methods for environmentally friendly ocean cleaning after chemical or oil spills, based on marine-derived natural products;
- development of alternative energy sources from natural substances, such as the production of biofuels from algae.



7.1 > There is as yet insufficient scientific knowledge about bacteriophages – viruses that are specialized on bacteria as host cells. Ten billion of them can be found in a single litre of seawater.

Marine biotechnology had its beginnings in the 1930s. At that time, carrageenan and other polysaccharides (multiple sugars) began to be extracted from macroalgae and used in the production of food and cosmetic products. Four decades later, in the 1970s, scientists began to intensively search for and extract active compounds from mostly sedentary marine organisms such as sponges and cnidarians, but also from snails, bryozoans and tunicates.

The basics of genetics: how genetic information is encoded

The genetic information of every living organism is contained in its chromosomes. These are microscopically small filamentous components of every cell, whose structure and location vary and constitute one of the fundamental differences between viruses (not counted as living organisms), bacteria and archaea (prokaryotes, single-celled organisms without a cell nucleus), and plants, animals and fungi (eukaryotes, living organisms with a cell nucleus in the cell).

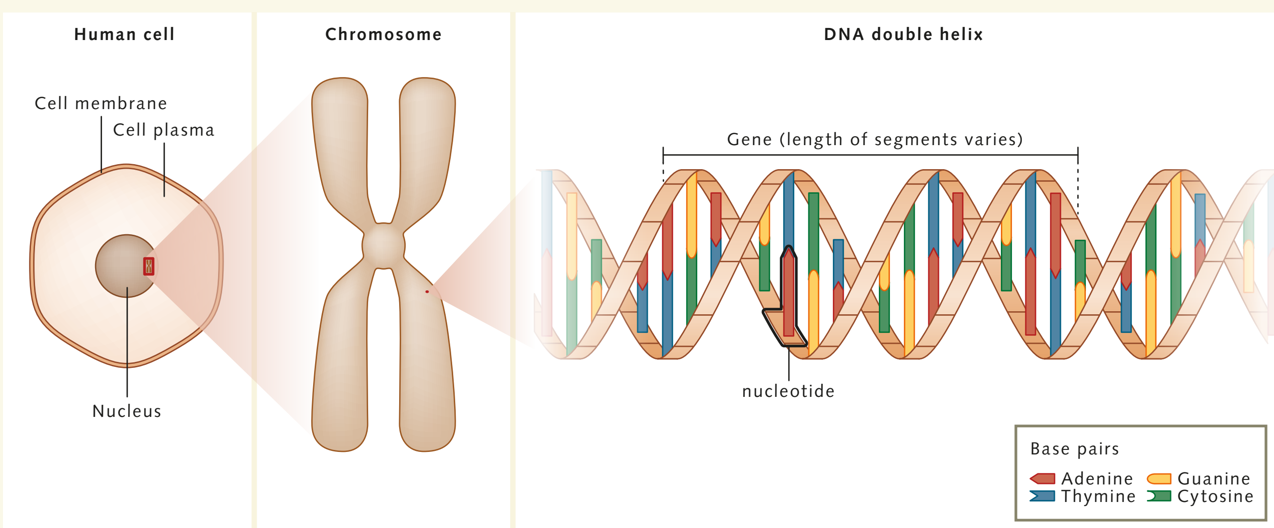
The chromosomes of viruses can consist of DNA (deoxyribonucleic acid) or RNA (ribonucleic acid). In prokaryotic unicellular organisms, only one ring-shaped chromosome made of DNA is found and this lies freely in the cell. In contrast, animals, plants and fungi have several chromosomes, often even a species-specific number of them. These consist mainly of DNA, but can also contain RNA and are located in the cell nucleus. This means they are enclosed by the membrane of the cell nucleus.

The chromosomes are nothing more than the tightly packed version of the long DNA molecule they are made of. If, for example, the 46 human chromosomes were to be unpacked, their genetic material in the form of DNA strands would come to a total length of about two metres. Each DNA molecule, in turn, looks like a twisted rope ladder. It consists of two parallel, interconnected polynucleotide chains. The backbone chains (the "ladder's" outer sides) consist of sugars and phosphates; the "rungs" consist of two interconnected nucleotide bases each, with exactly four different bases occurring in each strand, each of which combines with only one other to form a base pair – adenine (A) with thymine (T) and guanine (G) with cytosine (C). Because its two nucleotide strands wind around each other like a helix, the DNA molecule is also called a double helix.

A gene is a specific section of the DNA molecule that stores specific genetic information. Different species vary in the number of genes in their DNA. The human genome consists of an estimated 30,000 genes, while scientists have identified precisely 5416 genes in the bacterium *Escherichia coli O157:H7*.

If in the cell the information of a gene is needed for a certain process, the DNA double-strand splits at the relevant section. Free complementary RNA nucleotides from the cell now attach themselves to the exposed nucleotide bases of the DNA molecule: adenine to thymine, guanine to cytosine and vice versa. The only difference is that in RNA uracil replaces thymine as the complementary base to adenine. In this manner, the RNA nucleotides copy the DNA information and then, as messenger RNA (mRNA), migrate to the part of the cell where the information is needed.

There, in a process called translation, the mRNA is translated into a sequence of amino acids from which proteins are then produced and cellular processes can be set in motion. For this reason, mRNA is also called bioactive.



7.2 > A human's genetic information is stored in the cell nucleus, or more precisely in the 46 chromosomes whose individual DNA strands, strung together, would come to a length of two metres.

But research at that time and today's modern biotechnology are scarcely comparable: New deep-sea research technology, modern DNA sequencing, replication and chemical analysis methods as well as advances in bioinformatics have revolutionized this branch of research and generated step changes in knowledge. Today, marine biotechnology is a pillar of the "blue bioeconomy"; that is, entire economic sectors have it as their foundation. Experts speak of a golden era and estimate that by 2025, pharmaceutical and chemical products worth USD 6.5 billion will be traded worldwide, the origin of which can be traced back to the genetic diversity contained in the oceans.

New technologies revolutionize research

Deciphering the entirety of a living being's genes was first achieved in 1995, when the complete genome sequence of the bacterium *Haemophilus influenzae* was published. Only six years later, scientists almost completely decoded the human genome sequence. It consisted of approximately three billion letters (nucleotides) and raised the hopes of many experts that they may finally hold the key to understanding the complex human organism.

However, only a short time later, it became evident that deciphering the genome sequence of a living being is only a first big step, as the expression of genes depends on numerous environmental factors as well as the complex interplay of genes with each other and with the environment. Nowadays, experts use bioanalytical high-throughput methods, referred to as omics technologies, to elucidate these many interrelationships. These largely automated procedures allow for the parallel, comprehensive investigation of biomolecules contained in a biological sample in a relatively short time. They are named after the biomolecules investigated (genomics, transcriptomics, proteomics, metabolomics). This means that with their help, scientists not only sequence the complete genetic information of a living organism (genome), but can also decode the totality of all RNA molecules (transcriptome), proteins (proteome) or metabolites (metabolome) present in the cell at a given time.

These genetic blueprints are stored in digital form in genome databases and with the help of computer algorithms they can be analysed and studied in terms of their functions. Aided by high-throughput gene/genome sequencing methods, marine researchers not only identify a large number of microscopically small species that had previously always been overlooked in water samples. They also gain deep insights into the molecular basis of many life processes and an ever greater understanding of what has to happen for an organism to live and function in its characteristic manner. This knowledge then enables them to copy certain processes or blueprints, or else to rewrite gene sequences so that, for example, selected species of bacteria are able to produce a variety of medically effective substances to be used to manufacture pharmaceuticals.

If a living organism's genetic information is to be changed in a targeted manner, scientists use "genetic scissors", the CRISPR/Cas9 technology. They can use it to edit the genetic material of cells as desired, meaning they can specifically switch off genes, alter them or even replace them. Methods like this are referred to as genome editing. CRISPR/Cas9 actually works in all cells and all organisms, in humans as well as in animals, plants and microorganisms. Used together, omics technologies and genetic scissors therefore offer scientists almost unlimited possibilities to utilize marine genetic resources or to render them usable by means of targeted modifications of their genetic material.

These new technical possibilities also prompt desires. The better the marine gene pool is understood, the more frequently biotechnology companies apply for patents on potentially useful genetic information, thus securing exclusive usage rights for a certain period of time. When in October 2017 scientists investigated the number of patents now revolving around marine organisms and their genetic material, they counted 862 affected species and approximately 13,000 genetic sequences the use of which was protected by patent. The listed species ranged from marine giants such as the sperm whale *(Physeter macrocephalus)* and the giant oceanic manta ray *(Manta birostris)* to fish and mussels as well as tiny creatures such as

7.3 > Jellyfish, salps, crustaceans, worms, algae and thousands of other plankton species were fished out of the sea by researchers on the Tara Oceans Expedition (2009 to 2013) at more than 210 different locations. Their genetic material is now being analysed using modern high-through-put methods.

How do CRISPR-Cas9 genetic scissors work?

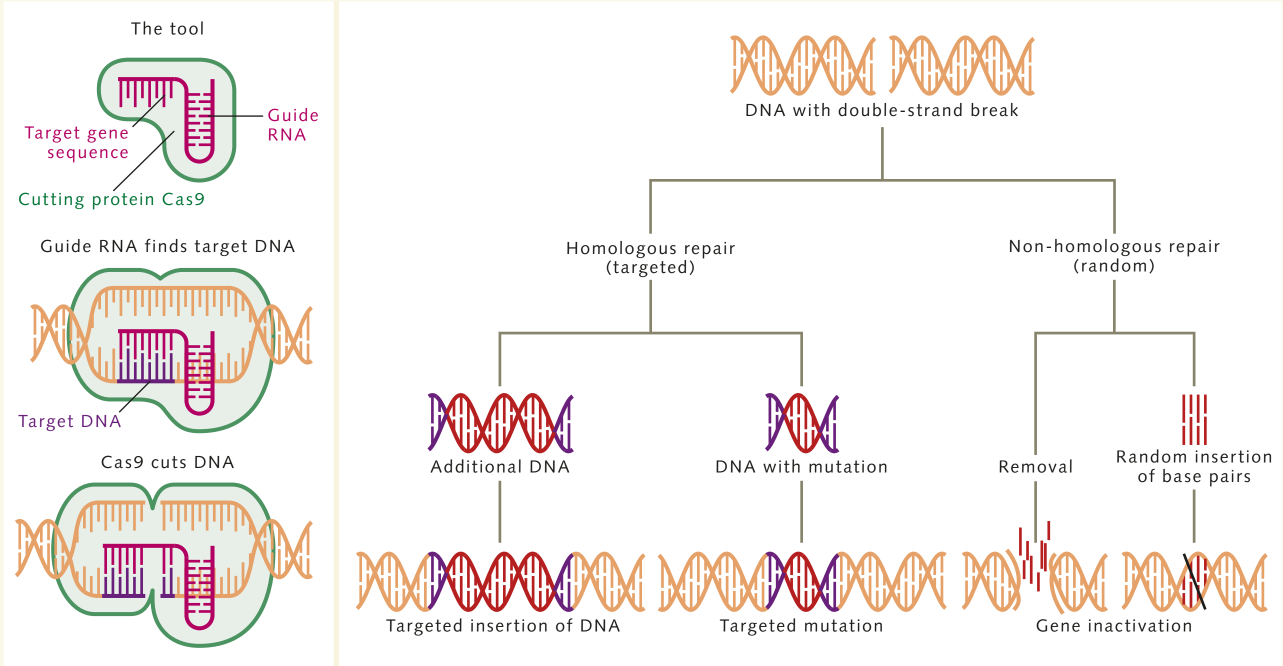
Programmable genome editing using CRISPR-Cas9 genetic scissors is a new molecular biological method allowing scientists to sever any DNA strand at a very specific point and, in the course of the subsequent repair, cut out, exchange or even insert individual DNA building blocks and thus rewrite individual genes.

CRISPR stands for "Clustered Regularly Interspaced Short Palindromic Repeats" and refers to sections of DNA repeats. The genetic scissors were developed by Emmanuelle Charpentier and Jennifer Doudna, two molecular biologists who were awarded the Nobel Prize for Chemistry in 2020 for their work on this technology.

The basic CRISPR-Cas mechanism originates from bacteria. It serves there as a kind of immune system, allowing the bacteria to recognize and fight off hostile viruses on the basis of previously stored DNA fragments. Scientists have now found ways to make use of this fascinating mechanism. In order to localize the site where the double strand is to be cut, the scientists provide the cutting protein Cas9 with a selected target sequence known as guide RNA. The protein then searches the double-stranded DNA for exactly this sequence. When it reaches the target sequence, in other words the cleavage site, it docks at the double-strand and cuts it.

Once Cas9 has cut the double strand of DNA, the cell's natural repair programme kicks in and rejoins the severed ends. This repair can be random (non-homologous) or targeted (homologous). In the case of non-homologous repair, individual DNA building blocks are removed or incorrectly assembled at the cleavage site. As a result, the gene in question can no longer be read correctly and is therefore no longer active. In homologous repair, a new gene segment or a short new DNA sequence can be inserted at the cleavage site and the gene function can thus be altered.

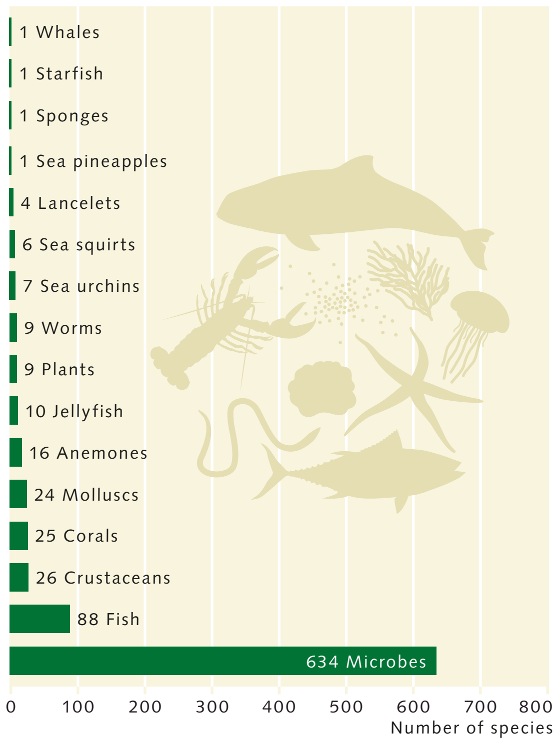
Both the guide RNA and the cutting protein Cas9 are produced synthetically and then introduced into a cell. Compared to other genome editing methods, the CRISPR-Cas9 genetic scissors are easier, faster and more cost-effective to use. This method is also far more precise than others: unintentional cuts in the DNA strand are rare and can largely be ruled out. Moreover, CRISPR-Cas9 can be used to make several changes to the genome simultaneously.



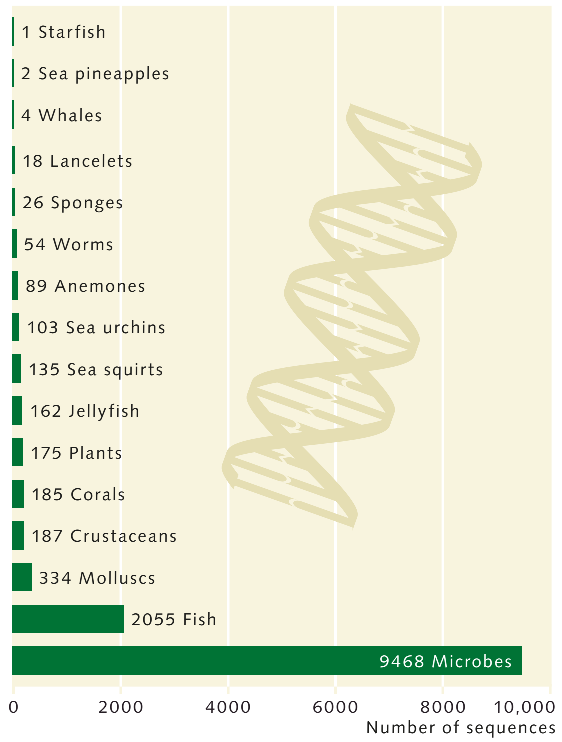
7.4 > The CRISPR-Cas9 genetic scissors are a molecular biological method for cutting and modifying DNA with pinpoint accuracy. The method can be used to insert, remove or modify individual DNA building blocks. It works with all organisms and is used in animal and plant breeding as well as in biotechnology.

7.5 and 7.6 > In October 2017, scientists investigated the number of patents registered for genetic information of marine organisms at that time. They counted 862 affected species and approximately 13,000 genetic sequences the use of which was protected by patent.

Marine species with patent sequences



Patent sequences from marine species



archaea and plankton. Ninety-one of the listed species were deep-sea dwellers, especially species occurring in biocoenoses at hydrothermal vents.

The patents surveyed had been filed by a total of 221 companies. However, almost half of the patents were held by a single large corporation, the German chemical company BASF, even though BASF itself does not conduct marine research. This major corporation and its subsidiaries instead search the public gene databases for promising sequences and check their commercial potential. The analysis also showed that the majority of patent claims were made by institutions from only 30 countries and the European Union. The remaining 165 countries of the world virtually did not appear in the statistics.

The great diversity of marine organisms means that basically every single species holds genetic information that could potentially be commercially exploited in one way or another. Biotechnologists and chemists are currently primarily looking for bioactive molecules that can be used as pharmaceutical compounds, as food supplements, as fertilizers or energy sources, as raw materials for the production of cosmetics and for various other industrial applications.

Medicine from the sea

The success story of medicine from the sea began in 1945, when a young chemist named Werner Bergmann was diving off the coast of Florida and discovered an inconspicuous, previously unknown brown sponge in shallow water. A colleague of Bergmann's scientifically described the Caribbean sponge and gave it the Latin name *Cryptotethya crypta*, today also known as *Tectitethya crypta*. Werner Bergmann extracted two previously unknown organic substances from the sponge – spongothymidine and spongouridine.

At that time, the chemist already suspected that these substances could one day be useful in medical research. How accurate his suspicions were became evident in particular in 1987, when the US Food and Drug Administration (FDA) approved the first drug to treat the immunodeficiency disease HIV. The drug was called azidothymidine (AZT) and its structure was modelled on the two substances that Werner Bergmann had extracted from sponge tissue more than 40 years earlier. Only two years after its approval, AZT had become the most expensive drug in the world. At that time, patients paid up to USD 8000 per year, which generated more than USD 100 million in annual profits for the manufacturing company.

Following Bergmann's example, scientists have discovered approximately 34,000 different secondary metabolites in marine organisms, many of which are of particular interest for pharmaceutical research. They kill bacteria or viruses for example, fight cancerous tumours and fungal diseases, strengthen the immune system, inhibit

7.7 > All marine organisms possess genetic information that can potentially be exploited. This table shows some of the most intensively researched groups of organisms, possible areas of application for their active compounds or extracts, and the greatest challenges to industrial use.

Source	Use	Representative phyla (exemplary genera/species)	Challenges
Metazoans	Medicine, cosmetics	Tunicates – Chordata *(Ecteinascidia turbinata)*, Mollusca *(Conus magus)*, sponges – Porifera *(Mycale hentscheli)*, Cnidaria *(Sinularia sp., Clavularia sp., Pseudopterogorgia sp.)*	Sourcing and supply sustainability
Macroalgae and seagrasses	Food, feed, medicine, cosmetics, nutraceuticals, biofertilizers/soils conditioners, biomaterials, bioremediation, energy	Rhodophyta *(Euchema denticulatum, Porphyra/Pyropia spp., Gelidium sesquipedale, Pterocladiella capillacea, Furcellaria lumbricalis, Palmaria spp., Gracilaria spp.)*, Chlorophyta *(Ulva spp.)*, Ochrophyta *(Laminaria hyperborea, Laminaria digitata, Ascophyllum nodosum, Saccharina japonica, Saccharina latissima, Sargassum, Undaria pinnatifida, Alaria spp., Fucus spp.)*, seagrasses *(Zostera, Cymodocea)*	Sourcing and supply sustainability, yield optimization, large-scale processing and transport, disease management
Microalgae	Sustainable energy, cosmetics, food, feed, biofertilizers, bioremediation, medicine	Chlorophyta *(Chlorella, Haematococcus, Tetraselmis)*, Cryptophyta, Myzozoa, Ochrophyta *(Nannochloropsis)*, Haptophyta *(Isochlysis)*, Bacillariophyta *(Phaeodactylum)*	Bioprospecting and yield optimization (1 – increase in biomass/volume ratio, 2 – increase yield of compound/extract production, 3 – Improve solar-to-biomass energy conversion)
Bacteria and archaea	Medicine, cosmetics, biomaterials, bioremediation	Actinobacteria *(Salinispora tropica)*, Firmicutes *(Bacillus)*, Cyanobacteria *(Arthrospira, Spirulina)*, Proteobacteria *(Pseudoalteromonas, Alteromonas)*, Euryarchaeota *(Pyrococcus, Thermococcus)*	Culturing for non-culturable species, yield optimization
Fungi	Bioremediation, medicine, cosmetics, food/feed, biofertilizers	Ascomycota *(Penicillium, Aspergillus, Fusarium, Cladosporium)*	Limited in-depth understanding, yield optimization
Thraustochytrids	Food/feed, sustainable energy production	Bigyra *(Aurantiochytrium sp.)*, Heterokonta *(Schizochytrium sp.)*	Limited in-depth understanding, yield optimization
Viruses	Medicine, biocontrol	Mycoviruses, bacteriophages	Limited in-depth understanding, yield optimization

inflammation or diabetes, lower the risk of heart disease or protect an organism from UV radiation. Chemists and pharmacologists working with marine-derived active compounds are now developing 2.5 times as many new drugs as the industry average.

The scientists often produce synthetic copies of the natural active compounds, meaning that not only can consistent quality of the active compound be guaranteed, but the substance can also be produced in sufficiently large quantities. Both are basic prerequisites for industrial application, which are rarely met by the original substances. The secondary metabolites usually only occur in such small quantities in the marine organisms in question that, for example, several tonnes of a selected sponge, snail or algae species would have to be caught or harvested to obtain just a few grams of active compound. And even then, there would be no guarantee that the specimens collected would indeed contain the coveted compounds, given that the production of the active ingredient often depends on the season and the interactions of various environmental conditions on site. Just a few metres away or a few weeks later in the year, these conditions may be completely different and the target organism may do just fine without the specific active compound.

For the same reason, the cultivation of marine organisms for targeted mass production of active ingredients presents major challenges. Attempts to keep sponges in aquaculture systems in order to produce active compounds have failed repeatedly. And even in modern laboratories, the complex natural marine living conditions can only be simulated inadequately. While some progress has been made – among other things in the cultivation of microalgae, whose secondary metabolites may prove useful in the development of antibiotics and cancer drugs – more than 85 per cent of all microorganisms are still considered unculturable.

Scientists are now also able to explain why sponges, cnidarians and other molluscs living on the seabed display such particularly high diversity of marine-derived active compounds. Once firmly anchored to the sea floor, these usually very long-lived animals are hardly able to escape – neither from intrusive neighbours who want to overgrow them, nor from predators, intrusive fungi or algae. The sessile animals therefore need to produce effective deterrent substances. They are actively supported in their production by highly specialized microorganisms with which they live in close symbioses. Scientists are therefore no longer surprised when it turns out that secondary metabolites found in tissue samples of a sponge or other mollusc actually have a bacterial origin.

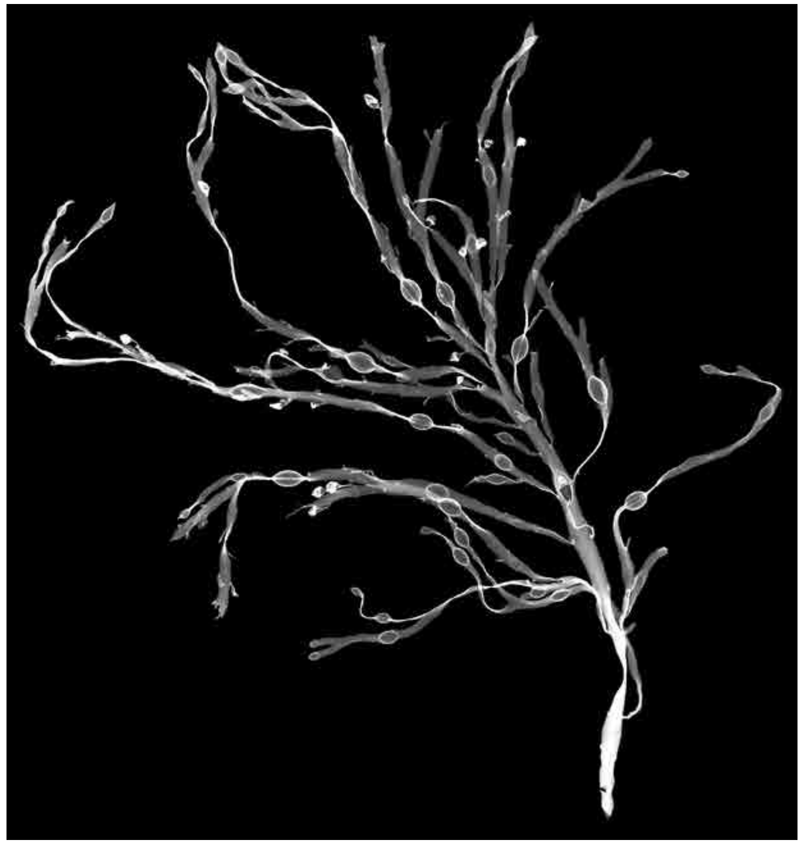
In some cases, however, marine organisms take up the secondary metabolites with their food. The antitumour agent Kahalalide F, for example, is now known to be produced by *Bryopsis spp.* algae – in very low concentrations. Scientists originally found this active compound in the sea snail *Elysia rufescens*. This species consumes Bryopsis algae and accumulates the compound in its body. Its concentration in the snail's tissue can be up to 5000 times higher than in the algae themselves.

Since the market launch of the antiviral drug AZT in 1987, the US Food and Drug Administration has approved a total of 13 pharmaceuticals containing marine-derived active compounds; globally there are 17 approved pharmaceuticals of marine origin (as of March 2021). The AZT models spongothymidine and spongouridine, for example, led to the development of the two compounds vidarabine and cytarabine, which are used in the treatment of blood cancer and viral infections. Researchers extracted the natural active compound ecteinascidin 743, also known as trabectedin, from the mangrove tunicate *Ecteinascidia turbinata*. A replica of this active compound is contained in the drug Yondelis, which is used to treat cancerous tumours.

Currently, an additional 23 drugs made from marine-derived active compounds are in the clinical trial phase. Pre-clinical studies are underway for 313 marine-derived active compounds, including eight anti-malarial compounds. Nearly two out of three of all new marine-derived natural products are now derived from microorganisms.

This highlights their increasing significance for biotechnology research. Given these statistics, experts have hailed marine biotechnology research a success story.

7.8 > Since the 1970s, the blue blood of the Atlantic horseshoe crab *(Limulus polyphemus)* has been used to test new vaccines for purity. It contains blood cells as part of the crabs' immune system that are particularly sensitive to toxic bacteria. If new vaccines are contaminated with such bacteria, the cells attack the bacteria and form clots. The good news for the animals is that there is now a synthetic alternative to their blood.



7.9 > The Baltic brown alga *Fucus vesiculosus* contains 44 effective components of interest. However, their quantity or concentration fluctuates through the seasons. The alga produces some active compounds mainly in winter, others almost exclusively in summer.

Normally, researchers have to extract, purify, identify and study the biological activity of around 15,000 different secondary metabolites in order to find the one active compound that will eventually be approved as a drug. The marine researchers' success rate stands at 17 approvals out of 34,000 secondary metabolites. However, the development of pharmaceuticals from natural substances remains a very expensive and lengthy process. It usually takes 15 to 20 years before a drug is approved.

Nevertheless, commercial interest in genetic material from the sea is growing steadily. Industrial research on natural products is, however, mainly driven by medium-sized and smaller pharmaceutical companies. Despite the vast potential of marine-derived natural products in particular, but also terrestrial natural products, most large corporations closed their natural product research departments in the 2000s in favour of "blockbuster drugs". These promised fast and high profits through large market shares. Today, large corporations often pursue a strategy of closely following the progress made by research companies and buying up these mostly smaller companies as soon as they can present initial promising results. If the large corporations invested directly in basic research, the pharmacologists' and chemists' yield rate would certainly be quite a bit greater still.

Use in cosmetics production

Due to their many positive properties, marine-derived natural products are often used in the production of cosmetics. These are frequently derived from marine bacteria, microalgae or fungi. However, there are also products on the market containing active compounds produced from macroalgae, fish and corals. Manufacturers are particularly interested in substances such as:

- Amino acids that protect marine organisms from high UV radiation near the ocean surface. The cosmetics industry often advertises these as anti-ageing compounds;
- Substances called exopolysaccharides; these are multiple sugars secreted by various microorganisms. When used as cosmetics, they increase the skin's moisture content;
- Carotenoids (fat-soluble pigments) and polyphenols (secondary phytochemicals), which have antioxidant or anti-inflammatory properties, slow down the skin's ageing process and make it more resistant to environmental factors;
- Enzymes and peptides that protect the collagen stores in the skin and in this way also slow down skin ageing.

Alginates (salts of alginic acid) and the polysaccharide fucoidan from brown algae, chitin from the carapace of shrimp, powder from oyster shells, carrageenan from red algae, collagen and gelatine extracted from jellyfish and fish are all widely used in the cosmetics industry. But manufacturers also use extracts from microalgae, fungi, soft corals and deep-sea microorganisms to create products that are supposed to prevent the formation of wrinkles, moisturize the skin and slow down its ageing process. Despite the great variety of products, scientists assume that the cosmetics industry is far from knowing and using all the marine active compounds. According to the scientific community there is still plenty of room for new discoveries.

Marine-derived natural products as food and feed additives

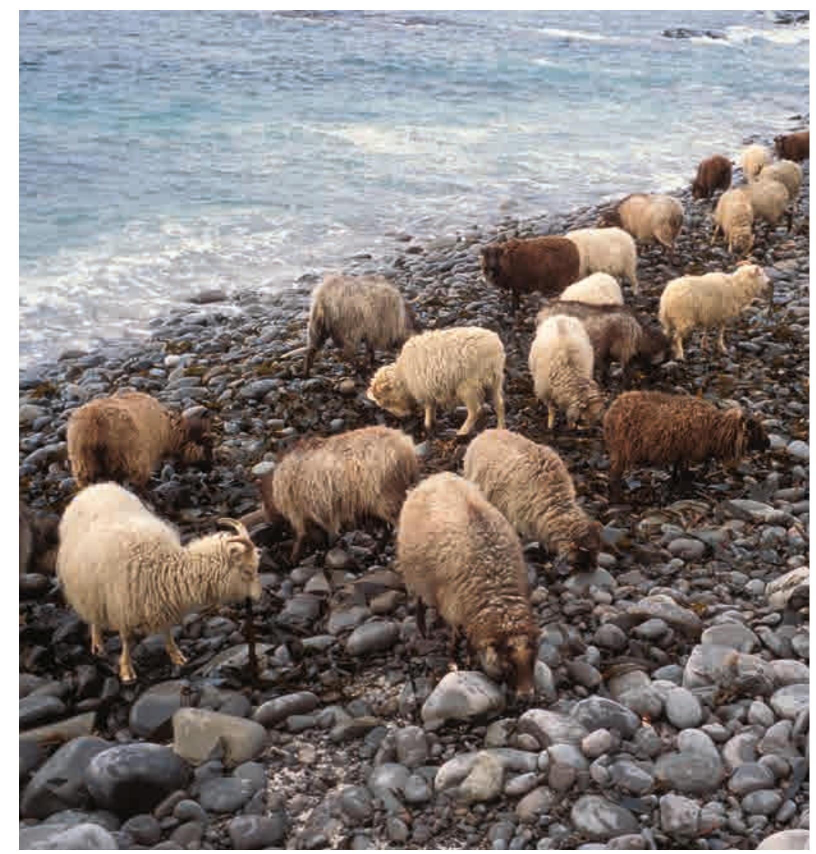
Their functional diversity makes marine-derived natural products a popular additive in food and feed production. Chemical components obtained from fish waste, microalgae and macroalgae, marine bacteria and fungi are used in the industry as natural preservatives, pigments, stabilizers, thickeners and binding agents, as food supplements and as prebiotics. Foods with bioactive additives are said to have a wide range of health-promoting effects. Food and beverage manufacturers also use cold-active enzymes from marine organisms in the production of heat-sensitive products. These enzymes prevent, for example, temperature-related changes in a product's smell, taste, appearance and feel. Antifreeze proteins are used to improve the quality of frozen foods. They prevent the formation of ice crystals and are produced, among other organisms, by algae living in sea ice. This property allows the algae to survive the long polar winter undamaged.

Manufacturers of fish feed are currently urgently searching for alternatives to fishmeal and fish oil and microalgae might give them what they are looking for. Selected species produce not only the essential fatty acids, which are vital yet cannot be produced by the human body, but also amino acids, which are needed to ensure the health and good growth of farmed fish. Moreover, microalgae are the main food source of saltwater crayfish (Artemia), rotifers (Rotifera) and copepods (Copepoda), which in turn are needed as live food for fish larvae. Researchers are working on optimizing the microalgae. The aim is for them to produce so many essential fatty and amino acids that both the zooplankton and, in the next step, the fish larvae can grow most favourably.

Possible applications in agriculture

Seaweed is the prime candidate for use in agriculture. Scientists are currently investigating its suitability as a fertilizer and animal feed as well as a raw material for biogas production, which in turn can be used as fuel (bioethanol) or for electricity generation. Small farmers in many coastal regions have always used washed-up macroalgae as a natural soil conditioner. Regularly applied, seaweed improves the soil structure as well as the humus content and thus the soil's nutrient content. Nevertheless, scientists see scope for improvement. Among other things, they hope that controlled composting of the algae could accelerate their subsequent release of nutrients to the soil and the crops growing therein. If this were successful, com-

7.10 > On the Scottish Orkney island of North Ronaldsay, a breed of sheep feeds almost exclusively on seaweed and kelp washed up on the rocky coastline or which the animals can reach at low tide.



7.11 > Workers rake up Sargassum seaweed, huge carpets of which have recently been washing up on Caribbean beaches where they rot away. In Mexico alone, the army and volunteers removed more than 57,000 tonnes of smelly heaps of seaweed in the summer of 2019.

posted macroalgae could replace conventional fertilizers. The vast quantities of Sargassum, a genus of brown macroalgae, which the sea now regularly washes up on the coasts of the islands and ocean-facing countries in the Caribbean, could potentially be used in this way. When the algae carpets rot in the surf zone, they not only harm the tourism industry but the nutrients released also overfertilize the sensitive coastal ecosystems and severely damage the coral reefs. In some instances farm animals also accept macroalgae as a feed. In this respect, the sheep on the Orkney island of North Ronaldsay are certainly a special case: seaweed is their main food source.

Microalgae and cyanobacteria also hold great potential. They produce biostimulants that promote the growth, development and resilience of crops such as cereals. These biostimulants include polysaccharides, minerals, vitamins, oils, fats, acids, pigments and hormones. Extracts from microalgae are therefore increasingly used as biofertilizers in farming.

Chitin is extracted from the shell of the Arctic prawn *(Pandalus borealis)* and used to produce chitosan. Chitosan binds fats and suspended solids and is therefore not only used in medical products and food supplements, but also in wastewater treatment plants as well as in the beverage industry in a variety of large-scale applications. In agriculture, chitosan can serve as a coating for fertilizers, pesticides, insecticides and herbicides and, due to its properties, ensure that nutrients or toxins are released into the soil in a controlled manner. Seeds and leaves can also be coated with chitosan to protect them from microbial attacks.

Aids for dealing with environmental pollution

The genetic diversity of marine organisms offers us humans a wide range of tools for detoxification and for the elimination of environmentally harmful pollution, a process known as bioremediation. Metabolites produced by sponges are used as anti-fouling agents in the fight against algal growth on ship hulls and other surfaces. Various strains of bacteria are able to break down hydrocarbons, aromatics and carbohydrates at a particularly fast pace and are thus suitable for cleaning up soils or marine regions affected by oil spills. Scientists are also aware that certain marine microorganisms produce enzymes that can break down plastics and other petroleum-based synthetic materials. However, the mechanisms and extent of such decomposition in the marine environment and the manner in which these processes can be used in the fight against marine litter are still being studied.

Enzymes from marine fungi are used to clean soils polluted with copper and zinc. The same substances are also used to decolourize textiles or paper. Microalgae and macroalgae are known to filter nutrients, heavy metals and even pharmaceutical compounds from seawater. As it is relatively cheap to grow macroalgae and seagrasses, these are being considered for large-scale use as biofilters in wastewater treatment. Microalgae, in contrast, are already in use today to combat heavy metal contamination. Purification by means of microalgae is a two-step process. First, the algae adsorb the heavy metals, i.e. the toxic substances accumulate on the tiny organisms' cell walls. Then the algae absorb the heavy metals into their cells and neutralize their toxic effect with the help of metal-binding peptides (organic compounds).

Marine-inspired materials

Marine-inspired natural materials bring with them a number of desirable properties: they are salt-tolerant to a certain degree, withstand high (water) pressure and endure heat as well as cold. Depending on their provenance, they may also possess previously undiscovered physical, chemical or biochemical properties. Experts believe that marine-derived natural products could, for example, be put to excellent use in the development of materials for medical applications. Examples would be materials for the production of artificial heart valves, bone implants or artificial joints.

However, there are still some hurdles to be overcome before this becomes feasible. For example, processes are needed that allow for the target substances to be isolated and prepared at the requisite high quality. It must also be ensured that sufficient quantities of the required substances are available at all times and that the properties of these source substances do not change over the course of the seasons.

Economically interesting sources of new biomaterials include algae, jellyfish, sponges, tunicates, mussels and crustaceans. They contain polysaccharides, enzymes, lipids (water-insoluble natural substances), pigments, minerals, ceramic materials (bioceramics) and toxins that could quite possibly be utilized in medical applications. Bioactive ceramic materials, for example, are extracted from corals, calcareous shells and sea urchins. They are then used as source materials for the production of hydroxyapatite, which is the main component of the inorganic substance in bones and teeth.

Glass sponges also serve as a model for designers and developers. These form a skeleton of needles, also called spicules (singular spiculum) that consist of highly pure silicon oxide, which the sponges form with the help of enzymatic processes from dissolved silicon in the surrounding seawater. Experts are trying to imitate these processes in order to use the material obtained for medical or optical applications. Silicon-containing materials are also used in high-tech products in the fields of microelectronics and optoelectronics.

In the search for alternatives to plastics and other petroleum-based synthetic materials, scientists are banking on macroalgae and microalgae. Cleaned, treated, dried and pressed into shape, macroalgae can be used as disposable tableware, for example. Various substances contained in the algae can also be used to make foils and other packaging materials. Carbohydrate-rich macroalgae and microalgae could also serve as a starting point for the production of polylactides.

To date, most biodegradable plastics are made from these synthetic substances. However, since polylactides decompose very slowly, scientists are still searching for better options.

Who should benefit from the marine gene pool?

There are numerous potential areas of application for marine natural products (MNPs) – and much of the genetic diversity contained in the ocean has not been decoded at all. This raises a multitude of questions. For example, who should benefit from the marine gene pool? Should the benefits accrue solely to states which fund this costly research? Doesn't the ocean belong to everyone? How should access to the sea's precious genetic resources be regulated at the international level – and what can be done to ensure that despite more intensive human use of marine resources, conserving biological diversity is the focal point of all action?

The search for answers to these questions starts with the United Nations Convention on the Law of the Sea (UNCLOS). It establishes the legal framework for all human activity in and on the oceans and seas, covering topics such as research, utilization of resources, and conservation of the marine environment, including – albeit without mentioning this specifically – biodiversity. Crucially, UNCLOS defines which maritime zones are classed as national territorial waters and are thus administered by the coastal states, and which parts of the ocean are defined as Areas Beyond National Jurisdiction (ABNJs).

The water column in the maritime regions beyond the limits of national jurisdiction is referred to in UNCLOS as the "high seas", while the adjoining seabed is known as "the Area". In relation to marine genetic resources, the distinction between national and international waters or areas is critical, since there is already a binding international treaty on terrestrial and maritime zones under national jurisdiction, namely the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) (abbreviated to "Nagoya Protocol"). The Protocol was adopted by the international community at the 10th meeting of the Conference of the Parties to the Convention on Biological Diversity (CBD) in October 2010. It entered into force on 12 October 2014 and to date (April 2021) has been ratified by 130 countries.

The Nagoya Protocol was initially negotiated with the intention of establishing rules which ensure that profits arising from access to and utilization of genetic resources and the traditional knowledge associated with them are shared with their respective countries of origin in a fair and equitable manner. As the Protocol's underlying principle, each state has the sovereign right to determine access to the genetic resources originating on its territory. However, the Protocol also aims to ensure that access to such resources is possible under fair and transparent conditions. It therefore stipulates minimum standards which states must consider when developing their national regulations.

The Protocol is also informed by the principle that countries of origin have a right to share fairly and equitably in the benefits arising from utilization of their genetic resources. Here too, the Protocol establishes guidelines under international law.

At the same time, it obliges all Parties to ensure that access to and extraction of genetic resources are in compliance with any permit requirements adopted by the country of origin. The terms and conditions applicable to benefit-sharing must be negotiated with the country of origin prior to any extraction of material.

In practice, however, these legal provisions create a considerable administrative burden: if scientists from one country wish to extract marine genetic resources from another country's national waters, an application must be lodged and approval obtained beforehand – in addition to, and separately from, the diplomatic research permits that are also required.

Furthermore, the issue of what form any subsequent benefit-sharing will take must be regulated with the supplier country months or even years before any research is conducted. Options include not only monetary remuneration but also the sharing of research results, the inclusion of local scientists in research projects, or the provision of training for junior scientists. Inclusion and training are fundamentally positive as they promote international scientific cooperation and motivate coastal states in species-rich maritime regions to actively protect their coastal waters.

7.12 > The needle-like spicules forming the skeleton of glass sponges such as the species *Pheronema giganteum* consist of highly pure silicon oxide, which the sponges form by means of enzymatic processes from silicon dissolved in seawater. Experts are trying to mimic these processes in order to use the material thus extracted for medical or optical applications.

Access solely for cash? The dispute over public genetic databases

Until now, most of the genetic information that researchers have decoded has been made available by them via publicly accessible digital sequence information (DSI) databases. This genetic information is useful for conducting comparative analyses and is vital for biodiversity research, as well as for research on natural products and active substances. Pharmaceutical companies and other businesses use these freely available gene sequences to identify active substances, register patents, develop new products and generate profits. However, they are under no obligation to remunerate the data producers or the country of origin of this genetic material – a fact which has outraged an army of critics worldwide in recent years. As a result of their protests, a debate is currently under way about the implementation of the Nagoya Protocol and how the economic benefits arising from the use of this data can be shared in a fair and equitable manner at the international level. Restrictions on access and payment of fees are options being discussed.

The German National Academy of Sciences Leopoldina is opposed to restrictions on access. According to a statement released by the Academy, to enable free research worldwide, DSI databases must continue to be openly accessible. The coronavirus pandemic, in particular, has shown that the exchange of sequence information, in this case of novel pathogens, contributes significantly to scientific progress. In addition, DSI databases are a key tool for biodiversity conservation because, for example, changes in ecosystems can be tracked with their assistance.

The Academy's experts are in favour of equitable sharing of benefits arising from the use of biological diversity; however, this must be done in a way which does not jeopardize either biodiversity conservation or Open Science. The situation is also complicated by the fact that, to date, information on the geographical origin of the data is missing for almost half of all digital sequence information. The scientific community should therefore develop solutions to make this information traceable in the databases in the future.

Ideas on how to resolve this dilemma have been developed by an Open-Ended Working Group under the Convention on Biological Diversity (CBD). The framework developed by the Working Group will be discussed at the 15th meeting of the Conference of the Parties to the Convention on Biological Diversity in Kunming, China, in October 2021.

At present, however, the usefulness and effectiveness of the Nagoya Protocol are often still undermined by the differences in the Parties' implementation of its provisions.

In some countries, the application and authorization procedures relating to the Protocol are so complex and time-consuming that scientists abandon the research projects concerned or, where feasible, relocate them to maritime regions under other national jurisdictions, or to international waters. Others opt to focus on researching their own domestic waters instead.

A new agreement should provide clarity

The scientific community's experiences with the Nagoya Protocol rules, described above, play an important role in negotiations on the governance of genetic resources from international waters. As the reader will recall, the high seas cover more than two-thirds of the ocean and more than 40 per cent of the Earth's surface. They are the largest ecosystem on Earth and therefore also the largest reservoir of species diversity.

Under UNCLOS Articles 256 and 257, all states, irrespective of their geographical location, have the right to conduct research in international waters, both in the water column (high seas) and on the seabed (the Area). Theoretically, then, states or corporations could carry out marine scientific research in these international waters at any time, extract active substances from the sampled material, reproduce these substances and use them to develop pharmaceuticals or other revenue-generating products – without sharing any of the profits with other countries.

In order to prevent conduct of this nature, the United Nations General Assembly decided, in December 2017, to elaborate a new legally binding additional protocol under UNCLOS to regulate not only the conservation of marine biological diversity in areas beyond national jurisdiction in general terms but also the utilization of marine genetic resources in these areas. Its official title in English is: International legally binding instrument 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 (BBNJ).

After several years of preparation, an intergovernmental conference, involving representatives of all the UN member states, was convened for the negotiations. To date, three formal sessions of the conference have been held; a fourth session, which was postponed from 2020 to 2021 due to the coronavirus pandemic, has not yet taken place. Although an initial draft of the instrument is now available, progress in the negotiations has been limited so far. One of the contentious issues is whether the water column, like the seabed, in international waters forms part of the common heritage of mankind, such that all the world's countries should benefit from potential revenues arising from it. This argument is presented mainly by developing countries which cannot afford to fund their own costly marine scientific and deep-sea research. Many developed nations, by contrast, argue that the water column in the high seas is not part of the seabed; they claim that the benefit-sharing requirement established by the International Seabed Authority (ISA) for profits from deep-seabed mining does not apply in the water column.

The position adopted thus far by the European Union (EU) is that sea areas beyond national jurisdiction (ABNJs) are part of the global commons – in other words, they form part of the common-pool resources that may be utilized by all nations of the world. Nonetheless, as regards the commercial utilization of genetic resources from ABNJs, compensation for non-participant countries should be considered; feasible options, from the European Unions' perspective, include scientific cooperation, training programmes for marine researchers from developing countries, and support for the establishment of a marine science infrastructure in these countries. Compensation payments as a form of benefit-sharing are rejected by the European Union, however.

Alongside all these fundamental questions, a series of detailed issues is hampering the negotiations. For example, how can it be ensured that all nations are kept fully informed about who is extracting genetic material from international waters, where they are doing so, and what happens to this material? To date, the discussion has focused on the establishment of an information and cooperation platform (clearing-house mechanism), e.g. for mandatory notification of planned research projects and the provision of a form of match-making service for potential partners. There is also some debate about the establishment of formal policy and science bodies and a secretariat, tasked with monitoring and coordinating compliance with all the provisions of the future agreement.

There is still a lack of clarity, however, on the powers to be granted to these individual bodies and where the secretariat might be located. It is likely that a separate Conference of the Parties (COP) will be established under the new agreement; representatives of all the signatory states would convene in this forum on a regular basis to review the implementation of the agreement, adopt any amendments that may be necessary, or regulate further details.

A further open question relates to sampling and how it can be proven that the biological material collected genuinely originated in international waters. In the case of organisms that are attached to the seabed, this question may be relatively easy to answer: the coordinates of the place of extraction would presumably suffice. In the case of plankton or migrating shoals of fish, however, determining the place of origin is more difficult. In such cases, is it, once again, the place of sampling that counts, or is the determining factor the location where a marine organism first saw the light of day, if this is known at all? The latter option is favoured mainly by states whose coastal waters are particularly species-rich and whose mangrove forests, reefs and seagrass meadows serve as a nursery for numerous marine species. However, a conclusive answer to this question is still awaited, along with solutions to issues of international patent protection and its validity for patents on gene sequences from the ocean.

It is also important to note, at this juncture, that access to and utilization of marine genetic resources and fair compensation mechanisms are just one out of a total of four overarching topics to be regulated by the new instrument on the conservation and sustainable use of marine biological diversity in international waters. The negotiating package also addresses rules on:

- Area-based management tools (ABMTs), this includes marine protected areas;
- Environmental Impact Assessment (EIA);
- Knowledge and technology transfer.

These negotiating packages often overlap; this is the case, for example, with knowledge transfer and the debate about benefit-sharing for marine genetic resources. The challenge facing the chief negotiators is how to achieve a balance of interests across all four topics. With regard to marine genetic resources, it is crucial that all nations have the opportunity to carry out genetic research, to access international databases and to utilize the vast amounts of data that the latter hold for universal benefit. At the same time, the rules must be framed in a way which ensures that research can continue and is not excessively burdened by technical and administrative complexities. The international community must also ensure that:

- research and development in marine biotechnology are conducted in a sustainable manner;
- no ethical and social boundaries are transgressed; and
- all demographic groups – including the poorest of the poor and marginalized groups, e.g. indigenous communities – genuinely benefit from biotech solutions, including active pharmaceutical ingredients.

These objectives can only be achieved if knowledge, research results and commercial successes arising from marine genetic diversity are shared in a fair and equitable manner; if current rules on patent protection are reformed; and if policymakers collaborate constructively – and more intensively – with the representatives of business, science and civil society. As their most important shared task, they must take decisions relating to the conservation and sustainable use of marine biological diversity on the basis of current knowledge, align these decisions to universal needs and, above all, never lose sight of their common responsibility for the ocean and its biotic communities.

7.13 > Artisanal fishers such as these men from Myanmar often belong to the poorest demographic groups. The instrument on the conservation and sustainable use of marine biological diversity in international waters, currently being negotiated, must ensure that they too ultimately benefit from potential biotech solutions.

Conclusion

The dawn of a golden age

The ocean's biodiversity is unique. Exposed to sometimes extreme environmental conditions, marine life has found remarkable ways to adapt. The information underpinning their species-specific survival strategies is encoded in marine organisms' genetic material. It includes the blueprints for the secondary metabolites which marine fauna, flora, fungi, bacteria, archaea and viruses produce for a variety of purposes – and which often take great effect even in low concentrations.

Chemists and molecular biologists are therefore particularly interested in secondary metabolites. In their studies of marine organisms, they look for and extract these bioactive molecules and substances, describe their chemical structure, investigate their functions and seek to identify potential commercial applications as marine natural products or active ingredients. In doing so, they make use of modern DNA sequencing, replication and chemical analysis techniques, enabling them to undertake rapid and comprehensive analysis of sampled material and digitally store all the genetic information that it contains.

These new technological options have sparked something akin to "gold-rush fever" in the interrelated branches of marine natural product chemistry and marine biotechnology. Experts now assume that every single marine organism may contain genetic information with potential for some form of commercial application in the future. The experts are calling this a "golden age" and project that the global market for chemical and pharmaceutical products derived from marine genetic diversity will reach an estimated USD 6.5 billion by 2025.

Marine natural products and substances are already found in a wide variety of applications. For instance, they are active ingredients in 17 licensed pharmaceuticals and are used in food supplements and fertilizers. They also provide raw materials for cosmetics manufacturing and various other industrial applications. However, their immense potential raises a number of issues that will need to be dealt with soon. The three most important questions are the following: Who should benefit from the ocean's genetic resources? How can these potential active substances and any profits generated from their commercial use benefit humanity as a whole? And finally, with commercial interest increasing, how can marine biodiversity be protected effectively?

Proposed solutions to the issues surrounding the access to and sustainable use of genetic resources from maritime areas under national jurisdiction are set forth in the Nagoya Protocol, an agreement in international law. In practice, however, they are proving difficult to implement, encumbering rather than encouraging research.

Rules governing international waters are currently being developed – at the United Nations level – as part of a new global agreement on the conservation of biodiversity in international waters. The negotiations on this agreement have been ongoing for years, and the current COVID-19 pandemic has further delayed the process. Furthermore, due to technological progress, the need arises for new items to be constantly added to the agenda. What kind of compromise will ultimately be reached by the international community? Will it fuel this "gold-rush fever" – or will it establish tight restrictions in the interests of marine conservation? Only time will tell.