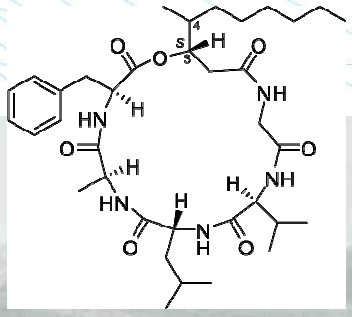
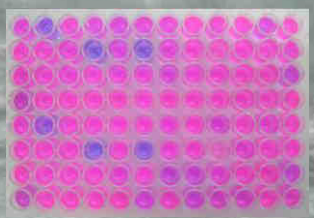
KiWiZ

The Kiel Center for Marine Natural Products at the Helmholtz Centre for Ocean Research GEOMAR

A research platform for marine natural product research and marine biotechnology





The KiWiZ

A research platform for marine natural product research and marine biotechnology

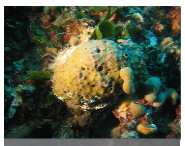
Kieler Wirkstoff-Zentrum
am Helmholtz-Zentrum für Ozeanforschung GEOMAR

The Kiel Center for Marine Natural Products
at the Helmholtz Centre for Ocean Research GEOMAR

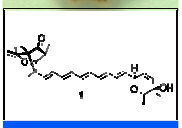
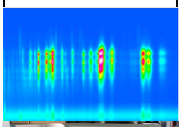
About KiWiZ

Dear reader,

What exactly represents KiWiZ and how did this develop during the past years? Reading about KiWiZ, the Kiel Center for Marine Natural Products, may give various impressions and expectations in your mind. In order to provide information on history and activities of KiWiZ we have written this brochure.





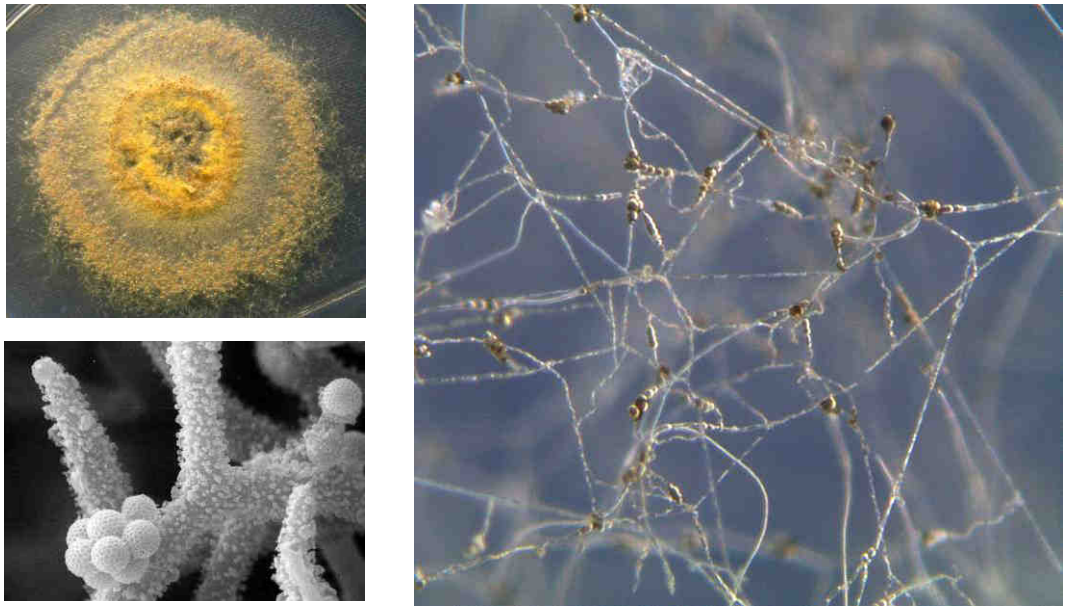



The idea for KiWiZ was born in summer 2004 at a local meeting to announce the programme on “Sea our Future” of the state Schleswig-Holstein. After several discussions, a project proposal was submitted and despite the change of the government in Kiel in 2005 the project was granted and started in December of the same year. The project was named “Zentrum für Marine Wirkstoffforschung im IFM-GEOMAR Kiel”. The project funding was first for 2 years and aimed to install the basic structures such as laboratories and scientific equipment and second for 3 further years until December 2010. Due to generous sponsoring by a local industrial partner from Schleswig-Holstein, the project generated its own logo and homepage in 2007. It changed its name to “Kieler Wirkstoff-Zentrum KiWiZ am IFM-GEOMAR” (Kiel Center for Marine Natural Products at IFM-GEOMAR).

The KiWiZ project essentially was a research activity of the Research Unit Marine Microbiology within Research Division 3 of IFM-GEOMAR and followed two previous research projects on marine natural product research. Other activities of Marine Microbiology were related with deep sea hot vent and cold seep microbiology and with various aspects of marine microbial diversity including the development of functional gene approaches to study microbial communities and the diversity of functional groups such as nitrifyers, sulfur oxidizers and photosynthetic bacteria. During the KiWiZ project time, additional research projects followed and extended the KiWiZ activities. In the public they were promoted and perceived as projects and activities of KiWiZ, though they were formally projects of IFM-GEOMAR and later GEOMAR with principal investigators from the small Marine Microbiology Research Unit. The KiWiZ was established with a slender format having a single head and multidisciplinarity at the scientist level. You may keep this in mind by reading this brochure.

I hope you enjoy the following short outlines on marine natural products in general and on KiWiZ in special.

Yours faithfully, Johannes F. Imhoff



Marine fungi are potent producers of biological active natural products. They form fascinating structures and have mycelia with manifold and characteristic sporangia and spores. The figure shows a colony of the fungus *Auxarthron conjugatum* (upper left) and ascospores of this fungus (lower left) and formation of chlamydospores of an unidentified marine fungus (right).

Content

Mission and Aims

KiWiZ is a platform for natural product research specifically from marine microorganisms covering aspects from the habitat to the hit for drug candidates and aims to include research on ecological aspects of natural products as well as on their biotechnological production. It essentially studies the biology and chemistry of marine natural products and their producers, marine bacteria and fungi. The exploration of the marine microbial biodiversity with respect to natural products, the development of methods for their biotechnological production with minimised risks for nature and man as well as their sustainable use is considered by KiWiZ.

The focus of the KiWiZ at GEOMAR is on identification, production and promotion of new natural products from marine microbial sources and the investigation of their biological activities and ecological function. Studies of the KiWiZ include all aspects from sampling, isolation and identification of the microorganisms in order to describe biodiversity, their preservation in culture collections, revelation of genomic potentials, as well as the extraction, purification, structure elucidation and characterisation of natural products from the cultured bacteria and fungi in order to describe and understand chemodiversity of marine microbes. In addition, optimisation of production conditions and scale up to a pilot scale for biotechnological production of bioactive natural products are considered as part of a sustainable approach for marine biotechnology. The research of KiWiZ relies on the extremely high diversity of marine microorganisms either newly cultured with special intention or contained in the large culture collections of KiWiZ containing marine bacteria and fungi covering more than 15.000 isolates, with a high proportion of new and unknown taxa. Important aspects became the growing panel of biological assay systems, in which suitability for specific applications is tested and the establishment of a substance library of pure marine natural products. With its unique setup and resources, the KiWiZ has developed into an excellent scientific centre on new natural products from marine microorganisms, being operated by an interdisciplinary team of scientists. Basic aspects on biology and chemistry of marine natural products as well as applied research topics are considered. It is a research platform for studies on the biology and chemistry of marine natural products and offers continuous supply from marine microbial sources into early drug discovery.

With its expertise in marine natural product research, KiWiZ represents a significant aspect of the marine biotechnology in Schleswig-Holstein, Germany and Europe. The KiWiZ is engaged in partnerships with local, national and international academic research facilities and commercial enterprises to promote natural products to the market for pharmacy, cosmetics, plant protection and food development.

Challenges of Marine Natural Products and Marine Biotechnology

The need for novel substances for the treatment of severe human diseases such as cancer, microbial infections and inflammatory processes, combined with the recognition that marine organisms provide a rich potential source of such substances supported the intensive search for new substances from marine organisms during the past decades. The remarkably high hit rates of marine compounds in screening for drug leads makes the search in marine organisms highly attractive. Natural products in general play an important role in the development of drugs. Covering the period from January 1981 to the middle of October 2008 68% of anti-infectives (antibacterial, antifungal, antiparasitic and antiviral) and 63% of drugs used in the cancer treatment were naturally derived (Cragg et al., 2009).

The oceans are the largest ecosystem on earth. They cover more than 70% of its surface and contain almost 80% of species on earth. Thus the oceans bear most of biodiversity on earth, the greatest part of which is still unknown. In addition, marine samples reveal a much higher hit rate for antitumor and antibiotic activities. These are very good reasons to intensively study and explore marine biodiversity for new drug candidates. It is now well recognised that in particular the diversity of chemical structures from marine and microbial sources is the greatest (Grabowski et al., 2008). Therefore, it is expected that in the future the major part of this pipeline will be filled from substances of microbial origin.

During the past decades, numerous advances in the marine natural product research led to a number of substances of marine origin being on the market as drugs or in advanced stages of the drug pipeline. The highlights of marine natural products in the pipelines of pharmaceutical products are summarised in several recent reviews (Imhoff et al., 2011; Mayer et al., 2010; Gerwick and Moore, 2012).

Quite astonishingly, the immense diversity of microbes in the marine environments and their almost untouched capacity to produce natural products, and therefore the importance of microbes for marine biotechnology was realised on a broad basis by the scientific communities only recently. This has stimulated world wide research activities dealing with the exploration of marine microorganisms for biotechnological applications, which comprise the production of bioactive compounds for pharmaceutical use, as well as the development of other valuable products, such as enzymes, nutraceuticals and cosmetics.

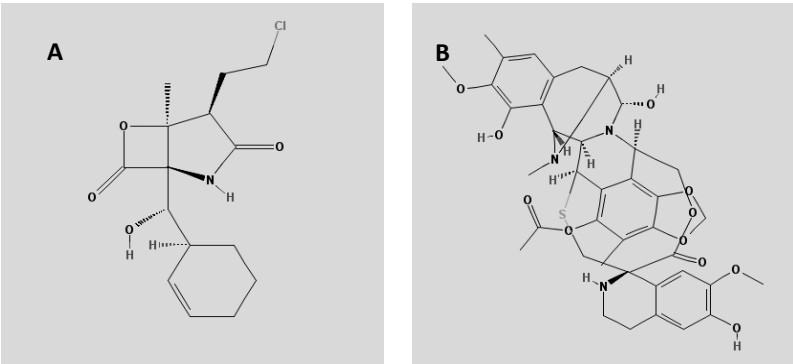
Scientific Background – why Marine Natural Compounds?

The marine ecosystems are largely unexplored, understudied and underexploited in comparison with terrestrial ecosystems and organisms. Hence, the potential for discovering new taxa, new structures and new bioactivities is very high.

Highlights in Marine Natural Product Research

Over the late decades of the last century, studies on marine natural products largely involved the collection of organisms from the sea, their extraction and the analysis of these extracts. Numerous new compounds have been isolated and many were found with interesting biological activities, most of which were described from sponges, corals and other marine invertebrates. However, the application of many promising substances was hampered by disappointing difficulties regarding reproduction and scale up. In addition, problems to supply sufficient amounts of the pure substances limited further progress in many cases. Recovery rates of substances such as halichondrin, ecteinascidin or bryostatin of less than 1 g from a ton of marine organisms as well as widely unsolved problems with the mariculture of most marine macroorganisms made it extremely difficult to produce substances in amounts sufficient for further studies (for review see Molinski et al., 2009 and Mayer et al., 2010). Only few marine natural products, for which alternative production processes became available, entered preclinical or clinical trials. For the current pipeline of marine natural products and for a comprehensive discussion of the success stories see Imhoff et al. (2011).

Marine microorganisms came into focus of natural product research only recently. Though microorganisms from terrestrial sources have been in focus for many decades already, for some unknown reasons microorganisms from the sea have been largely neglected for a long time. Besides pioneering work from the group of W. Fenical, systematic approaches to use marine microorganisms for biotechnological purposes and drug development were initiated only quite recently. Today it is realised that marine microbes represent an incredible huge reservoir of so far unknown bioactive substances.



Examples of current highlights of marine natural products on the market or in advanced stages of the clinical pipeline. A) Salinosporamide A, B) Trabectin (Yondelis®).

Marine Microbial Biodiversity

The oceans bear an almost unbelievable large diversity of microorganisms (DeLong, 2007). Marine microorganisms inhabit all kinds of available niches from the polar ice to hydrothermal vents, from the deep biosphere to mangrove forests and from the oligotrophic open ocean waters to polluted coastal waters and sandy beaches. A particularly attractive ecological niche for many microorganisms is the surface of macroorganisms such as algae, sponges, fishes, and corals. In numerous cases, bacteria and other microbes live in close association with higher organisms and form mutalistic or symbiotic relationships. It is realistic to assume that today we know less than 0.1 %, probably only 0.01 % (Simon and Daniel, 2010) of all microbes in the oceans. More and more evidence is accumulating on a habitat-specific composition of microbial communities. This includes for example specific differences in communities found on the surface of different algae (Lachnit et al., 2009), between different parts of the phylloid and rhizoid of a single alga species *Saccharina latissima* (synonym *Laminaria saccharina*) (Staufenberger et al., 2008), and between cortex and inner part of the sponge *Tethya aurantium* (Thiel et al., 2007).

Recent molecular approaches on the analysis of marine metagenomes have revealed a large number of phylogenetic lines of so far uncultured groups of bacteria and archaea (DeLong et al., 2006; Simon and Daniel, 2009). In addition, in the recent past a remarkable large number of newly described bacterial and archaeal taxa are of marine origin. Most important, we can hardly imagine the biotechnological potential of the cultured and even less of the uncultured and unknown microbes still hidden in the oceans. It appears to be almost unlimited: **„Much of nature‘s treasure trove of small molecules remains to be explored, particularly from the marine and microbial environments“** (Newman and Cragg, 2007).

Microbes - the True Producers

Increasing evidence is now accumulating that microorganisms are the true producers of a number of potent drug candidates, which were considered to be products of invertebrate animals in the early days of marine natural product research and whose development was seriously hampered by the supply problem. Three outstanding examples shall demonstrate this.

One prominent example is represented by the bryostatins, which were first extracted from the bryozoan *Bugula neritina* (Pettit et al., 1982). Over many years all attempts of developing an economic production by mariculture and to provide sufficient amounts for the necessary studies failed. It was the discovery that genes for the biosynthesis of this compound family were found within a bacterium (but not in the bryozoan) associated with *Bugula neritina* which opened up new possibilities for the biotechnological synthesis of the bryostatins (Sudek et al., 2007). The endosymbiotic Gamma-proteobacterium *Candidatus* "Endobugula sertula" has not yet been cultivated, but molecular techniques enable heterologous expression and thereby further development as a drug. Currently, bryostatin-1 is in several phase I and II trials and is being assessed as an anticancer drug and an anti-Alzheimer's drug (http://clinicaltrials.gov 2011).

A second example is represented by the first antitumor compound from marine organisms that is on the market (Yondelis® by PharmaMar) and which was first extracted from the tunicate *Ecteinascidia turbinata*. Complicated production processes have been developed over decades to produce this compound in a combined fermentation and chemical synthesis process, because aquaculture failed to deliver sufficient material. For the commercial production, a bacterial product, safracin, was used as a starter molecule for the chemical synthesis. However, on the basis of structural similarities of ET-743 to bacterial secondary metabolites, it was hypothesized that also ET-743 is the product of a marine bacterial symbiont (Rath et al., 2011).

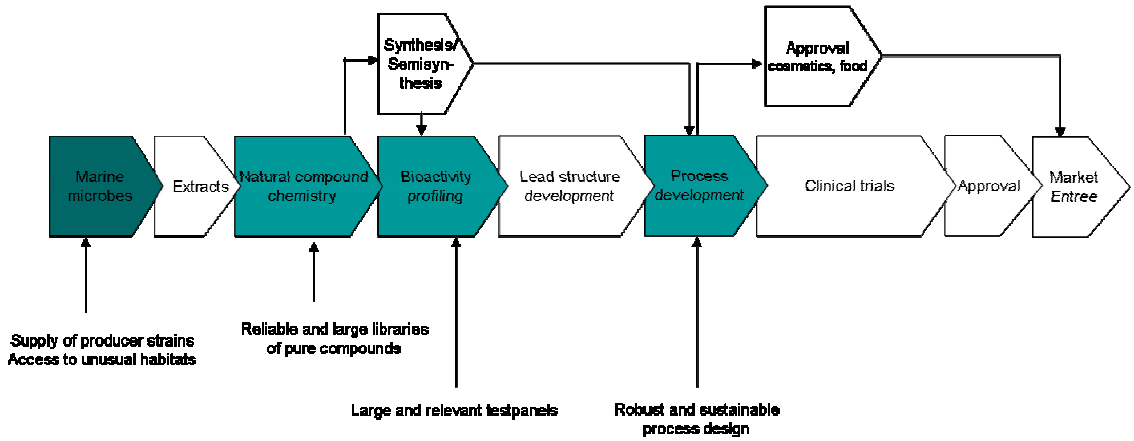
This holds also for the antitumor agent didemnin B from the Caribbean tunicate *Trididemnum solidum*, which was the first marine drug to be clinically tested in humans, but whose further development was hampered by the limited supply. Today, dehydrodidemnin B (called Aplidine®), a derivative thereof, is evaluated in various clinical trials. Quite recently, it was shown that the didemnins are bacterial products produced by the marine Alphaproteobacteria *Tistrella mobilis* and *Tistrella bauzanensis* and the putative didemnin biosynthetic gene cluster was identified in the genome of these bacteria.

These few examples give rise to the assumption that a greater number of natural products originally isolated from marine macroorganisms are indeed produced by microorganisms.

Marine Biotechnology of Natural Compounds

Marine Biotechnology. Marine biotechnology involves all aspects of the use of marine biological resources, either as the source for biotechnological applications or as the target. Facets of marine biotechnology range from off the shelf use of "-omics methods" in marine related R&D projects by academy and industry, through applications in products and processes in the industry, to the intricate development of the technology and knowledge itself. In the context of marine natural products, biotechnology includes all aspects of cultivation and harvesting biomass of the producer organisms, extraction and purification of the substances for further use. With sponges and algae this could mean cultivation in mariculture, with bacteria and fungi this means fermentation of the microorganisms in laboratory systems, extraction from cells and culture media and purification of the substances. Such biotechnological production is used in production of Yondelis® and Salinosporamid, two top candidates in the pipeline of marine drugs.

Providing processes for the production of bioactive compounds. Whenever marine natural products shall be used, it is essential to provide sustainable modes of supply, which include chemical synthesis or/and biotechnological production by the producer or improved strains thereof. Also, analogues of bioactive natural products with improved properties are relevant for drug development. A serious bottleneck in developing natural products from marine sources to pharmaceutical products during the past decades was the availability of biomass and/or of optimised cultivation conditions to gain sufficient amounts of substances for preclinical and clinical studies. Additionally, low amounts of isolated marine bioactive compounds, limited knowledge of their biotechnological production and limited feasibility of chemical (semi)synthesis are important bottlenecks hindering the entry of new marine substances into the pipeline. Discovery of new marine microbes and compounds and their maintenance have to be complemented by process design including purification, which is an integral part of metabolite production.



High added value chain from habitat to biotechnological product in marine biotechnology of natural compounds using microbes. Marine biotechnology leads to lead and process development and thereby provides the basis for e.g. pharmaceutical development. Upward arrows mark the necessary tools at the indicated steps. KiWiZ is a platform for all these tools.

The Political Frame - a Supportive Environment?

During the past two decades science politics in Europe put special emphasis on the evaluation of the perspectives of marine biotechnology for future scientific, economic and social developments in their countries and in Europe. Examples among numerous reports are “Sea our future” of Schleswig-Holstein and “Marine natural products in blue biotechnology” (Kube and Waller, 2003) and the Position Paper (No. 15) of the European Science Foundation on “Marine Biotechnology: A new vision and strategy for Europe”, which predicts that with the right actions taken now, Europe could be a world leader in the field of marine biotechnology by 2020 (Marine Borad, Børresen et al., 2010). **All of these studies have recognised marine biotechnology as an important science of the coming century, which is highly promising in aspects regarding scientific development as well as economic and social aspects.** They highlighted the special aspects of the marine natural product research as a promising field of the future.

Marine biotechnology market

Biotechnology in general is considered to be of growing importance for Europe and increasingly will contribute to shape the future of our societies. **Marine Biotechnology**, which involves marine bioresources for biotechnological applications, will fast become an important component of the global biotechnology sector. **The global market for marine biotechnology products and processes** is currently estimated at € 2.8 billion (2010) with a cumulative annual growth rate of 4-5 %. Less conservative estimates predict an annual growth in the sector of even up to 10-12 % in the coming years, considering the huge potential and high expectations for further development of this sector at a global scale (ESF Marine Board Position Paper 15, Børresen et al., 2010).

Blue biotechnology in the 7th EU Research Framework Programme

Marine and fresh-water biotechnology (blue biotechnology) is one of the research priorities of the 7th EU Research Framework Programme (2007-2013). Several calls have been related to blue biotechnology, though only a minor fraction (< 2%) of the budget devoted to “Food, Agriculture and Biotechnology” is deserved for this field. While marine biotechnology represents a large potential for European added value, the current level of collaborative research is not sufficient. Interdisciplinary cooperation and networking is needed. As it is realised trans-European collaboration will provide synergies and more value for money by a coordinated European funding, a preparatory activity was started in order to result in a future ERA-NET in marine biotechnology (CSA MarineBiotech). Additionally, special foci are set to the specific situation of the Baltic Sea, where the European Union's Baltic Sea Region Programme 2007-2013 promotes regional development through transnational cooperation including technological development.

In the following, the political and institutional situation of blue biotechnology on European, international and German level is summarised.

Major Challenges for Marine Biotechnology from an European View

The Position Paper of the Marine Board of the European Science Foundation provides a roadmap for European research in this field and sets out an ambitious science and policy agenda for the next decade (Marine Board, Børresen et al., 2010). It addresses five major research areas of marine biotechnology, one of which is concerned with health and the development of novel drugs, treatments, and health and personal care products. Because of its importance for Europe and European countries and in relation to the activities of the KiWiZ, the major aspects of natural products and health aspects of this report are shortly summarised.

Major challenges in the discovery of new drugs from marine biological resources were considered to be associated with identification of the marine resources (biodiversity), the efficient screening of compounds, securing access to marine resources and to the costs of drug development from natural products.

Biodiversity issue. The lack of taxonomic expertise for marine species was pointed out as a bottleneck, because very few experts in taxonomy of microorganisms exist. Efforts are needed employing both classical and molecular methods for species identification to speed up and make more efficient of marine biodiscovery.

Supply issue. The lack of sustainable supply of substances has stopped the further development of several highly promising marine compounds. The increased focus on marine microorganisms is in part due to the need to overcome the supply problem, because the fermentation and also the scale up of production processes using cultured microorganisms can eliminate the supply problem. Great improvements still have to be made in the identification, cloning, genetic manipulation and expression of biosynthetic pathways in order to apply these methods for production of identified natural products.

Technical issue. Most important, the novelty of bioactive compounds needs to be determined by dereplication to avoid “rediscovery of the known”. With pure compounds this can be achieved through interfacing spectroscopic information with databases (sensitive high-field NMR and accurate MS data). It was pointed out that methods should be used that are suited to the high-throughput screening platforms.

The search for new antibiotics has been declared as an urgent challenge. Multiresistance is recognised as a growing problem in treating infectious diseases. Nonetheless, industry has been reluctant in recent years to invest into research and development of antibiotics for several reasons. Also the World Health Organisation has identified antimicrobial resistance as one of the three greatest threads to human health. For these and a number of additional reasons the Position Paper recommends that special attention is given to the search for novel antibiotics from marine environments. Marine natural products, in particular those from actinobacteria and fungi were regarded as favoured sources of chemical diversity for the drug discovery.

International and European Marine Biotechnology Centres

Intensive attempts are made world wide to study the immense potential of marine biological resources and to make use out of it for human health and nutrition, for plant protection and other applications. Tremendous amounts of investments are related to these activities. Marine institutions and research centres with a focus on marine biotechnology and marine natural products from marine organisms were established all over the world. Many countries have recognised the importance of marine biotechnology and established research institutions and national funding programmes. Only a few outstanding examples of such activities can be mentioned here.

China has a national plan for bioscience and biotechnology out to 2050 and operates several research centres on marine biotechnology and natural product research e.g. at the Ocean University of China in Qingdao and at the South China Sea Institute of Oceanography with key disciplinary areas in sustainable utilisation of tropical marine biological resources and the Guangdong Province's Key Laboratories of Marine Drugs, and Applied Marine Biology. The Scripps Institution of Oceanography (USA in San Diego) with the Center for Marine Biotechnology & Biomedicine initiated important drug development projects during the past years with several substances in clinical trials. It is the world leading marine institution on natural products research.

The European Community is beginning to value the potential of marine resources, such as natural products, but lacks a coherent marine biotechnology research and technology transfer policy. Instead, some European countries support marine biotechnology with regional and national initiatives. Pioneers in this field are countries from Scandinavia and Great Britain. Only a few outstanding examples are mentioned:

The European Centre for Marine Biotechnology is a business incubator for new and emerging marine biotechnology companies and is co-located with the Scottish Association for Marine Science (SAMS) close to Oban in Scotland. It is home to Aquapharm Biodiscovery Ltd (founded 2000), one of the first UK marine biotechnology companies dedicated to the discovery and commercialisation of novel compounds from the marine microbes, a Culture Collection of Algae and Protozoa (CCAP), and GlycoMar, a marine natural products and drug discovery company.

The Marine Biodiscovery Centre (University of Aberdeen, UK) is another important centre for marine natural product research in Scotland.

The Marine Biotech Cluster in Tromsø (Norway) comprises organisations with a core business within the biotechnological use of marine sources as drugs, nutritional supplements, or products for aquaculture. A major initiative is the Centre on Marine Bioactives and Drug Discovery (MabCent-SFI) hosted by the University of Tromsø.

Marine Biotechnology and Natural Product Research in Germany

In contrast to a number of other European countries Germany currently lacks national efforts on a marine biotechnology initiative. In Germany research and development activities in marine biotechnology are scattered and studies on marine natural products lack a powerful institution to promote this topic. On the regional level, blue biotechnology has been recognised as an important field in Schleswig-Holstein and is part of activities formulated in a strategic "Masterplan Marine Biotechnology Schleswig-Holstein".

Though research on natural products is topic of the Leibniz Institute for Natural Product Research and Infection Biology-Hans-Knöll-Institute (HKI) in Jena and the Helmholtz Centre for Infection Research (HZI) in Braunschweig, marine natural products and their biotechnology are not in the focus of these institutions.

Research on marine biotechnology and/or marine natural products is a major and strategic part of just a few German institutions:

The **Fraunhofer Research Institution for Marine Biotechnology** in Lübeck has put its focus in the field of marine biotechnology e.g. on the isolation and utilisation stem cells of fish, on the use of fish cells as alternative of fish meal and on integrative aquaculture, but does not work on marine natural products.

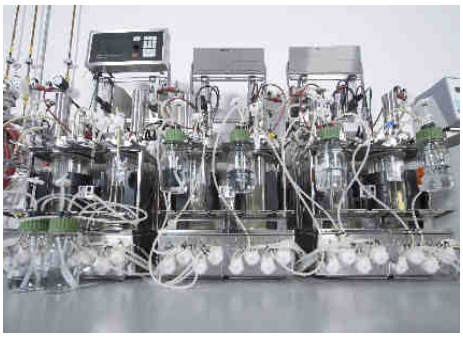
The **Institute for Marine Resources GmbH imare** in Bremerhaven has its focus on biosensor technology, technical applications of marine structures and nanomaterials, but does not perform marine natural products research. It was established in 2009 and is supported by finances through EFRE and from the state Bremen.

The **Institute of Marine Resources e.V. IMaB** in Greifswald exists since 1996 and operates with participation of members of the university Greifswald. It is build as a virtual institution organised in projects. Scientific activities include functional genomics, expression systems, natural products and marine enzymes.

The **Kiel Center for Marine Natural Product Research KiWiZ** is embedded in the Helmholtz Centre for Ocean Research GEOMAR and represents a minor activity of this centre. It was established in 2005 and financed through EFRE and the state Schleswig-Holstein until 2011 and is now an exclusive activity of the small Research Unit Marine Microbiology of GEOMAR. It is specifically focused on the research of natural products from marine bacteria and fungi and represents a major research facility of marine biotechnology in Northern Germany.

The KiWiZ - a Platform for Marine Natural Product Research




In December 2005 the starting point was set by State Minister Friedrich Austermann of Schleswig-Holstein (top) for the establishment of modern and well equipped laboratories for marine natural product research of the KiWiZ in Kiel-Kanal 44 (upper middle), including experimental fermentors (left lower middle). The large strain collections with capacities for liquid nitrogen storage (right lower middle) and a pure compound library depending on high capacity preparative HPLC systems and fraction collection (bottom right) are central facilities of the KiWiZ. A young and expert multidisciplinary team assured successful operation of the laboratories (bottom left).

The KiWiZ is Meeting the Challenges of Blue Biotechnology

The expectations on the commercial exploitation of marine microbial resources have initiated a dynamic development in marine biotechnology. In view of the increasing importance of this field and the lack of national initiatives within Germany, the state Schleswig-Holstein made major efforts for the foundation of the KiWiZ and substantially supported its establishment from 2005-2011.

The KiWiZ strategy was developed during 2004/2005 with the background of examples of highly active compounds found in marine organisms, the serious supply problem in mind, the problem of reproducibility, the recognition that some of the substances extracted from invertebrates may be the true products of associated microorganisms and that microorganisms represent a seriously under-investigated group of marine life. As the KiWiZ was established in the recognition of the major importance of marine microorganisms in natural product biosynthesis and their neglect in this field of research over past decades, it specifically deals with research on marine natural products from marine microorganisms, especially bacteria and fungi. Fungi as a whole and among the bacteria specifically actinobacteria are regarded as most potent groups of natural product producers and therefore the KiWiZ pays particular attention to these groups. The major focus is the development of marine natural products with biological activities for the treatment of human diseases, for applications in plant protection and in cosmetics.

The KiWiZ expertise and research profile is in line with the demands and research priorities pointed out by the ESF Position Paper 15:

> **"to increase basic research on taxonomy, physiology, molecular genetics and chemical ecology of marine species, in particular from unusual and extreme environments"**

The KiWiZ has long standing expertise in bacterial taxonomy and taxonomic identification is achieved for all strains selected according to their bioactivities. Molecular genetics are also applied for identification of biosynthetic pathways relevant to natural product biosynthesis. Access to unusual and extreme marine habitats is ensured through activities of the Marine Microbiology Research Unit.

> **"to improve technical aspects of the biodiscovery pipeline, including separation of bioactive substances, bioassays, dereplication strategies, and methods of structure determination"**

Significant improvement of the technical aspect is achieved in the KiWiZ due to the close coupling of chemical extraction and purification of compounds with the testing of bioactivities and early dereplication using HPLC- DAD/MS and data base information.

> **"to overcome the supply problem"**

In order to overcome the supply problem, the KiWiZ exclusively searches for bioactive compounds in bacteria and fungi cultivated under defined laboratory conditions which can be reproduced and scaled up to meet the demand for larger amounts of substances.

General Information and Research Strategy of KiWiZ

The KiWiZ is incorporated into the Helmholtz Centre for Ocean Research GEOMAR (formerly the Leibniz Institute of Marine Sciences) in Kiel. The formation of the platform was possible by fundamental financial support through the local government in Schleswig-Holstein, which supported the establishment of laboratory facilities, instrumentation and scientific personnel for marine natural product research for 5 years (2005-2010) and initiation of a pure compound substance library of marine natural products for 3 years (2008-2011) with altogether more than 8 Mio €.

With the notification of the grant approval in December 2005 the KiWiZ started officially its work as **a project of the Research Unit Marine Microbiology of the IFM-GEOMAR** (at that time). For the first year during whole 2006 provisional rooms were the basis to start the research work, while in parallel suitable laboratories were found, restored and installed during 2006/2007. In this year basic equipment for microbiological work and chemical analyses was established including HPLC/DAD-MS and liquid nitrogen freezer for strain preservation. In the following years, additional major equipment such as experimental and pilot scale fermentation systems (2008) was acquired and also a micrOTOF-II highly accurate mass detection system (2009) and several preparative HPLC-systems for substance purification.

The research strategy of the KiWiZ covers the whole high value added chain from the habitat to the biotechnological product in a research platform with a broad methodological range from microbiological techniques including microbiological community analysis and taxonomic identification, to natural compound chemistry including establishment of secondary metabolite profiles and chemical structure analysis, to genetic and genomic approaches, determination of biological activities and fermentation technologies and process development.

Large and unique strain collections and access to marine habitats are the basis for our research activities. The collections are described on page 17.

Bioactivity tests are carried out with a large panel which was established at the KiWiZ and is extended by assay systems provided by partners. It includes approx. 40 antibiotic assays with bacteria and fungi, including phytopathogenic ones and human pathogens, tests with tumor cell lines, and several assays with key enzymes involved in widespread diseases such as diabetes and Alzheimer's disease.

Chemical structure analysis uses analytical and preparative scale facilities including HPLC separation with DAD/MS detection, HPLC-ELSD, GC-MS, accurate mass determination with HPLC-DAD/HRESIMS, data base analyses (Dictionary of Natural Products, AntiMarin database, SciFinder) and take advantage of NMR instruments of the Otto-Diels-Institute for Organic Chemistry at CAU.

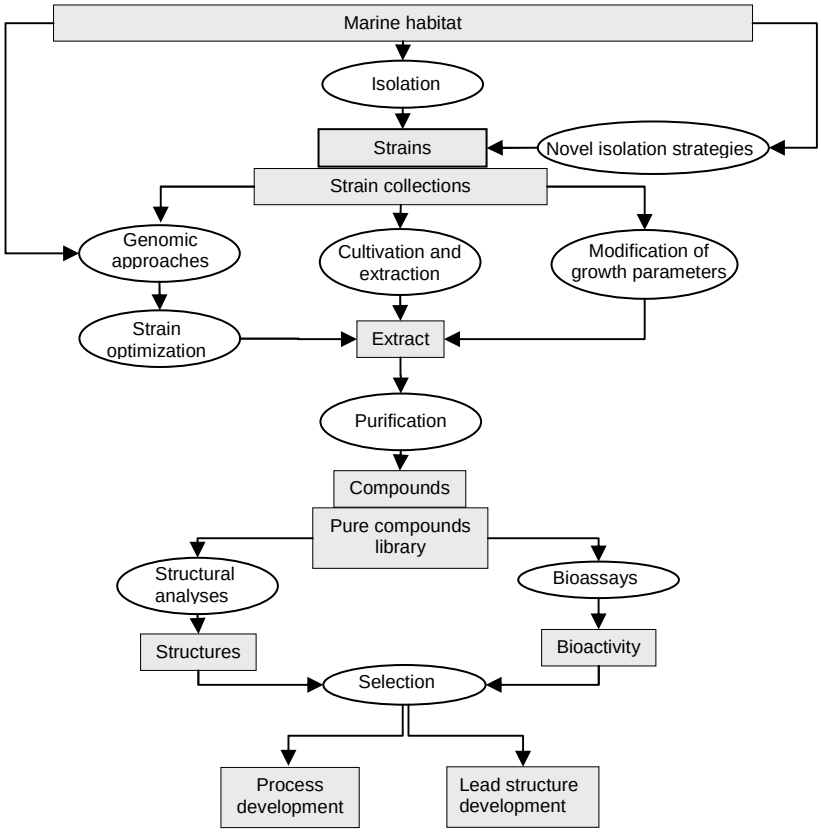
Process development technologies inclusive fermentation technologies at small scale experimental systems for process optimisation and a 250 L pilot scale fermentor for

biotechnological metabolite production with the necessary downstream processing, enable process development of substance production and purification.

A substance library is established containing highly purified natural products from marine bacteria and fungi, which is offered to external academic and commercial users. More information on this library is found on page 18.

KiWiZ has all facilities and laboratory capacity for marine biotechnology research. The required techniques are inhouse and if needed supplemented by external cooperations (e.g. NMR). The KiWiZ is operated by an interdisciplinary team of microbiologists, chemists, pharmacists and biotechnologists. Through the combined use of these different methodological approaches within one laboratory, a highly efficient research strategy is realised which meets the demands of the challenges in understanding the biological role of small bioactive molecules and employing marine microbes for blue biotechnology:

- To increase the number of available strains and genomic microbial resources by securing strain collections and biobanks. Emphasis is put on metabolic and genomic resources and on the discovery of their role in biological interactions.
- To understand the underlying regulation processes of the production of small molecules in order to control stimulation of biosynthetic pathways for biotechnological production.
- To secure availability, extension and maintenance of compound libraries.



Strategic outline of the research profile of KiWiZ for a sustainable discovery and development of marine microbial natural products.

Research Topics

Research on bioactive compounds has two major aspects. The first relates to the multiple biological functions bioactive compounds can fulfil. They may play a role in cellular and interspecies communication, signalling and in the defence of predators and pathogens and even may contribute in shaping the structure of marine microbial communities.

The scientific work of the KiWiZ aims to enlarge our knowledge on **the biology of natural products** by investigation of

- the diversity and potential of new marine natural products and their producers
- the role of bioactive compounds in marine microbial interactions
- the genetics and regulation of biosynthesis of marine bioactive compounds

The second major aspect related to marine natural products deals with the **potential use of bioactive compounds** in pharmaceutical applications, for crop protection, cosmetics and as food additives. Marine biological resources provided by the tremendous biological diversity of marine organisms, in particular bioactive compounds produced by the mostly untapped microbial resources offer a great potential for human uses. The exploration of these resources, the development of methods for their biotechnological production with minimised risks for nature and man as well as their sustainable use is included in our research strategy by:

- the analysis of the genetics of marine bioactive compound biosynthesis and their application to improve substance spectra profiles and production rates
- the analysis and evaluation of the biological activities of natural products as well as the development of new bioassay systems
- the development of biotechnological processes for the production of bioactive compounds

The performance of these research topics necessitates expertise in bacterial and fungal systematics, in natural product chemistry and structure analysis, in bacterial and fungal genetics and physiology, in pharmaceutical targets, in fermentation technology and process development. In addition, basic support is required to maintain microbial culture collections and the chemical substance library.

Small Bioactive Compounds – from Ecology to Marine Biotechnology

The biosynthesis of small biologically active compounds from marine bacteria and fungi is strictly regulated. They are produced under specific environmental conditions and are considered to play an important role in interspecies interactions and even in shaping the community structure of microbial communities. Such functions can relate to intermicrobial interactions and also in interactions between microorganisms and their hosts. Most important for the natural product research, microbial interactions can stimulate the biosynthesis of secondary metabolites not known previously and not produced under standard conditions of laboratory cultivation.

The following aspects are of particular importance for studies concerning the importance of biologically active compounds at their natural habitat:

- Selectional advantages to the survival of their producers
- Beneficial/deleterious effects on the hosts of the microbial producers
- Formation and inhibition of biofilms in marine habitats
- Establishment of specific associations of bacteria/fungi with their hosts and mediation of communication between microorganisms and their hosts
- Shaping microbial communities via action as signalling substances e.g. for the biosynthesis of other bioactive compounds.

In particular, microbial communities associated with sponges, macroalgae or bryozoa were intensively studied at KiWiZ both by genetic analysis with the 16S rRNA gene as marker molecule and by pure cultures investigations. Diverse microbial communities are associated with all of them and we have found not only species-specific association with different macroorganisms but also specific association of bacteria within a single sponge or alga. The role of small bioactive molecules in these interactions is an important aspect of future research at KiWiZ. Examples of this aspect are given below under “scientific highlights”.

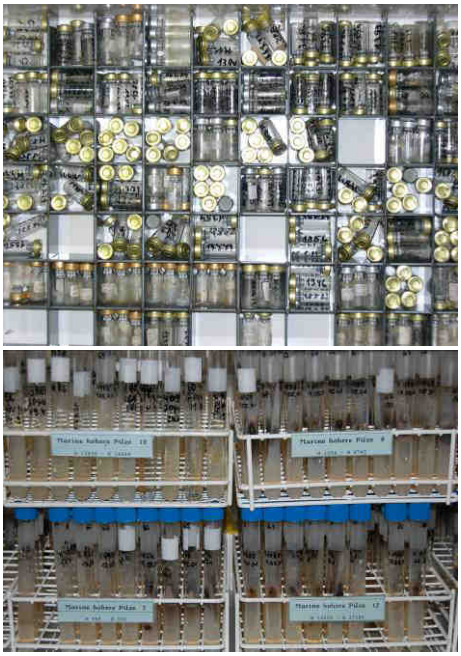
Small bioactive molecules are of particular importance in interactions between microorganisms. These include broad range and highly specific antibiotic interactions but also others, such as quorum-sensing inhibition and signalling in general. **The interactions between different microorganisms can be studied under laboratory conditions and may have relevance in the ecological context as well as in biotechnological processes for optimising the production of bioactive compounds.** Because little is known about this kind of microbe-microbe interactions and the biological function of microbial metabolites in marine habitats, this is an important topic of future research of KiWiZ. Thus, research on small biological active molecules from marine microorganisms provides great perspectives both for in depth ecological studies and for biotechnological applications.

Marine Biodiversity Conserved in Culture Collections of the KiWiZ

Large and unique strain collections of original environmental isolates and access to marine habitats are the basis for our research activities and represent invaluable resources.

In order to recover and maintain a broad spectrum of marine microbial diversity, the KiWiZ maintains large culture collections of both marine bacteria and marine fungi of approximately 15000 strains, which originate from all parts of the ocean. Different marine microbiologists have contributed to these strain collections during the past decades. Great biodiversity within these culture collections provides an enormous resource for the search of new bioactive substances. Though different ways of conservation are in use, the preferred mode is the conservation in liquid nitrogen, which ensures long term maintenance of viability and continued supply of constant strain material for sustainable production of metabolites.

In addition, the intimate interaction of the KiWiZ with the research group of Marine Microbiology at GEOMAR assures continued supply with new samples from all kinds of marine habitats, e.g. from the hot and warm deep sea, from the polar ice as well as from coastal areas and deep parts of the Baltic Sea, the Mediterranean Sea, the Atlantic Ocean, the Pacific Ocean and the Red Sea. With priority also samples from marine macroorganisms such as sponges, bryozoa, algae or others are used as sources. In order to isolate a broad spectrum of bacteria and fungi from selected unusual and extreme habitats, media and culture conditions for isolation procedures are modified.

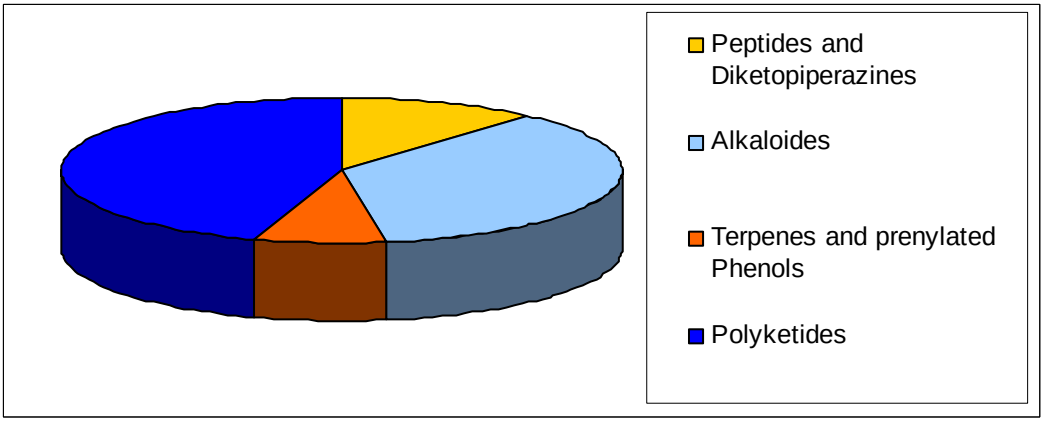


The preferred way of conserving bacteria as well as fungi is storage in liquid nitrogen (left). Among a number of other methods, lyophilisation (right top) and for shorter storage periods also agar slants (right bottom) are used.

The KiWiZ Library of Pure Marine Natural Compounds

The **library of pure compounds** has been built up in the frame of the SUBBITO project supported by the state government of Schleswig-Holstein and EFRE. Collections of pure natural compounds are rare, especially those comprising marine derived compounds. Here, the KiWiZ fills a gap with a high quality library. Compounds originate from KiWiZ scientific work and a comprehensive screening, which is continued. Only compounds with a purity of more than 80% and an amount of at least 10 mg are posted in the core library. Currently, several hundred compounds are stored in the collection. It has been approved that this library can be handled in high-throughput screening systems as other compound libraries originating from synthetical and combinatorial chemistry.

The KiWiZ library comprises a **high structural diversity**. Approximately half of the compounds belong to nitrogen containing structures like peptides and alkaloids, the other half are nitrogen free structures such as terpenes and polyketides.



The KiWiZ library of pure marine natural compounds comprises a high structural diversity. Among the alkaloids are e.g. indole-, pyridine-, chinoline-, chinazoline-, pyrrole-, and pyrazinealkaloides, phenazines, and derivatives of the tetramic acid. The polyketides comprise e.g. macrolides, chinones, xanthones, coumarines, pyrones, polyenes, and furane-containing structures.

Besides the compounds itself, data of the KiWiZ library are connected to virtual libraries, increasing the value of the compounds: For every compound, informations are stored in a comprehensive laboratory information and management system. The system comprises the origin and identification of the producer strain, the cultivation, the extraction procedure, the structure elucidation and biological activity of all compounds and ensures reproducible production of each compounds in amounts needed for further procedures. These sustainable procedures make the library of pure compounds very attractive for a broad range of applications such as drug development. Since its initial establishment in 2009-2011, the library is continuously filled with new compounds.
Because of the urgent need for new substances for the drug pipelines, the KiWiZ library is attractive and requested by colleagues and institutions, such as the Helmholtz Centre for Infection Research (HZI) in Braunschweig. It is also handled by the European Screening Port and used for various target systems, including new targets.

Achievements

Strong efforts were made for the sustainable exploration of marine microbial resources, in part from available large culture collections of marine bacteria and marine fungi, in part from newly isolated microorganisms from promising marine sources. Major achievements first of all relate to the establishment of the research platform, second on publication and patenting of the research results and third on fundraising for continuation of the work.

Establishing the research platform

- We started to secure the great culture collections of marine bacteria and marine fungi available at the Marine Microbiology Research Unit at GEOMAR by increasing storage capacity in liquid nitrogen and by reviving, identifying and storing many of the cultures in a database-managed culture collection.
- We established a large number of bioassays including antibacterial, antifungal, antitumor and several enzyme-based assays for the screening of biological active natural products.
- We established analytical and preparative HPLC-analysis for separation and purification of natural products
- We established methods and data bases for chemical structure analysis
- We implemented scale up of fermentation processes including down-stream processing
- We established a library of pure natural products of several hundred identified compounds with defined purity criteria for use by external partners

Publications and presentations

Research activities led to more than 60 publications during the last six years, including several review articles, and patents that are listed in the attachments. Some of these research aspects are shortly summarised as “Scientific highlights” in the next section:

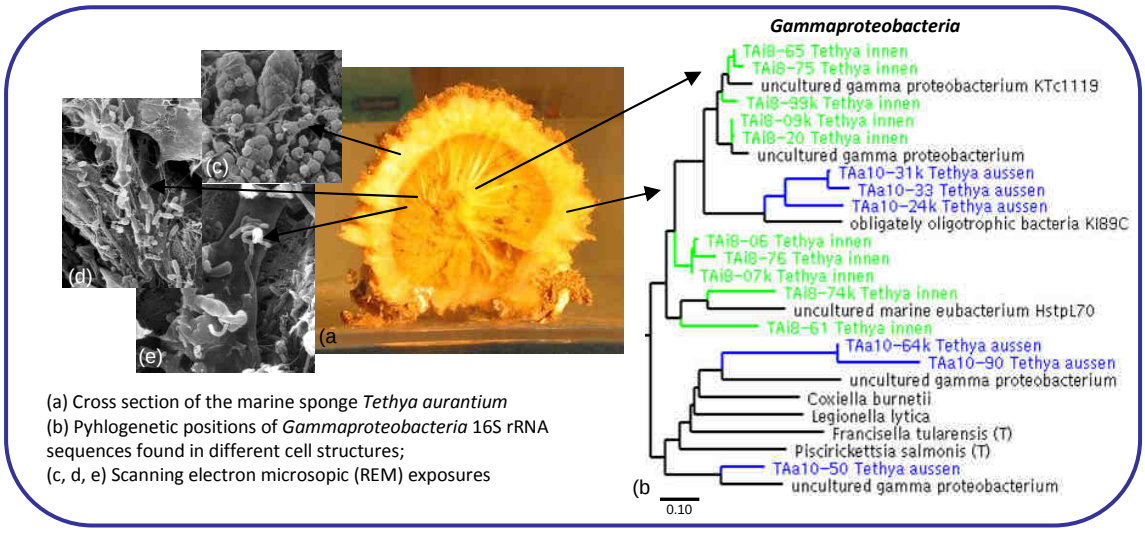
- a number of new bacterial species and genera (including a new family and order) have been described
- an increasing number of new natural products has been found and their properties were published
- marine microbial communities were evaluated for their potential of secondary metabolite production
- the ecological role of marine natural compounds was reviewed and discussed
- genetic tools were developed in order to improve screening strategies
- antitumor active substances and their possible application have been patented
- strategies for marine biotechnology in Europe were reviewed

The KiWiZ was very active in presenting its results on scientific conferences and workshops as reflected by the lists of posters and talks also given in the appendix.

Scientific Highlights - Examples of Research at KiWiZ

Spatial Association of Different Bacterial Communities in *Tethya aurantium*

Highly specific association of bacteria is demonstrated not only with particular sponge species but also with different types of cells in the Mediterranean sponge *Tethya aurantium*, which consists of two clearly different types of cells forming the exterior cortex and the interior endosome. *Tethya aurantium*, the sea orange, is characterised by a globular shape and a thick and well developed cortex, which is clearly distinguishable from the endosome by texture and colour of the tissue. Surprisingly, the bacterial community associated with this sponge revealed completely different bacterial communities present in the cortex and in the endosome. This was clearly shown in 16S rDNA sequences of clone libraries and their phylogenetic affiliation seen in phylogenetic trees as well as in banding patterns of denaturing gradient gel electrophoresis experiments. Members of a new sponge-specific cluster of 16S rDNA sequences affiliated to Betaproteobacteria were found in both cortex and endosome of *Tethya aurantium*. These bacteria presumably are specifically associated with this sponge. Other bacteria such as *Microscilla furvescens* were found to be associated with the sponge cortex only.



(a) Cross section of the marine sponge *Tethya aurantium*
(b) Pyhlogenetic positions of *Gammaproteobacteria* 16S rRNA sequences found in different cell structures;
(c, d, e) Scanning electron microsopic (REM) exposures

***Tethya aurantium* is unique in the clear differentiation of two bacterial communities associated with the cortex (blue clone sequence names) and the internal part (green clone sequence names). The specifically associated bacteria probably have adapted during evolutionary processes to the sponge environment.**

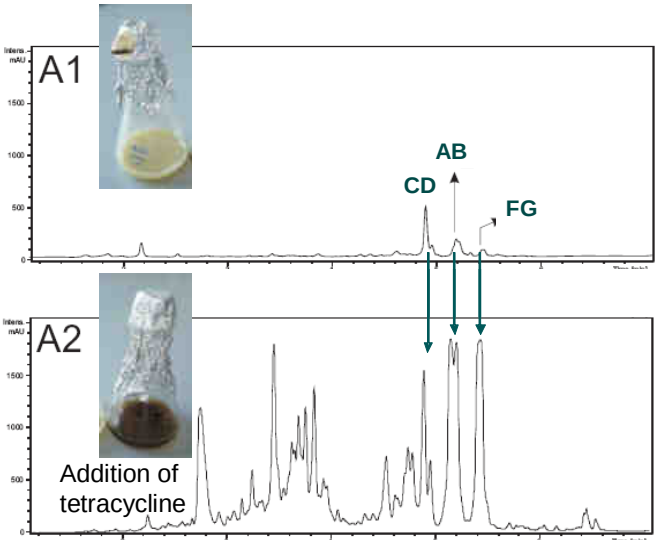
Thiel, V., Neulinger, S.C., Staufenberger, T., Schmaljohann, R. & Imhoff, J.F.: Spatial distribution of sponge-associated bacteria in the Mediterranean sponge *Tethya aurantium*. FEMS Microbiol. Ecol. 59, 47-63 (2007).

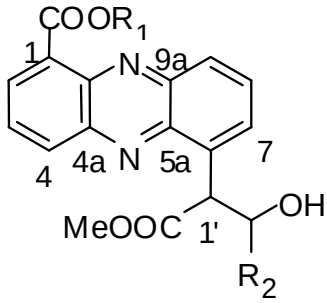
Antibiotics can Act as Signalling Substances

Subinhibitory concentrations of antibiotics were found to enhance and modulate the production of new phenazines, streptophenazine A-H, in a marine *Streptomyces* isolate. The streptophenazines differ in length and substitution of an alkyl chain. The pattern of metabolites formed depends on the antibiotic used. In the presence of tetracycline, streptophenazines F and G were induced and the production of streptophenazines A-D was increased. When using bacitracin, mainly streptophenazine H was produced. Streptophenazines C and H showed moderate activity against *Bacillus subtilis*, while streptophenazine C was also active against *Staphylococcus lentus*.

These findings like similar other studies demonstrate that antibiotics at subinhibitory concentrations may cause considerable transcriptional changes in various bacteria and that low antibiotic concentrations may lead to the augmentation of some adaptive characteristics.

Growing evidence supports the idea that antibiotics act as “chemical weapons” suppressing bacterial growth at higher concentrations, but at subinhibitory concentrations induce different responses which may have relevance for microbial interactions at marine habitats. Taking into account the specificity of bacterial responses to different antibiotics, it is suggested that they act at low doses as signalling molecules.



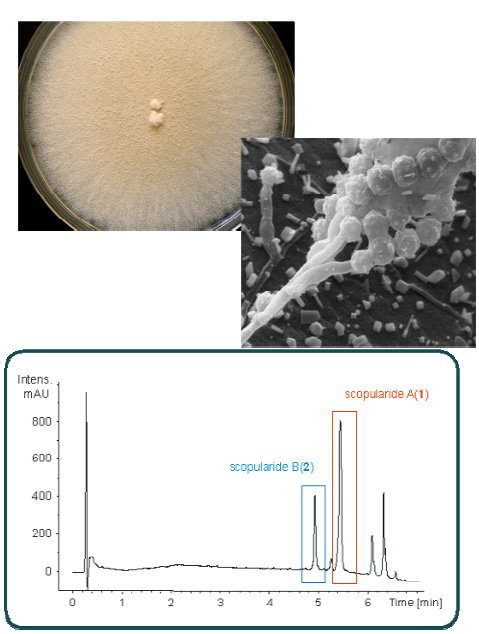


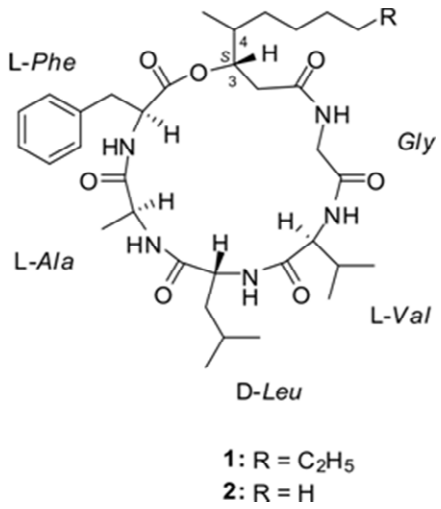
Chromatograms of extracts of a marine *Streptomycetes* strain (left, A1 without stimulation, A2 after addition of a subinhibitory concentration of tetracycline). Addition of subinhibitory concentration of antibiotics resulted in a dramatic shift in the secondary metabolite profile and the production of new compounds, the streptophenazines (R1 and R2 differentiate the various derevatives).

Mitova, M.I., Lang, G., Wiese, J. & Imhoff, J.F.: Subinhibitory concentrations of antibiotics induce phenazine production in a marine *Streptomyces* sp. J. Nat. Prod. 71, 824-827 (2008).

Antitumor Substances from a Marine Fungus are Patented

Two novel cyclodepsipeptides, scopularide A and B, were found in the fungus *Scopulariopsis brevicaulis*, which was isolated from the marine sponge *Tethya aurantium*. In addition, the known fungal metabolite paxilline was identified. The structures of the scopularides were elucidated by NMR, MS, and chemical derivatisation methods as cyclo(4-methyl-3-hydroxydecanoyl-Gly-L-Val-D-Leu-L-Ala-L-Phe) and cyclo(4-methyl-3-hydroxyoctanoyl-Gly-L-Val-D-Leu-L-Ala-L-Phe) for scopularide A and B, respectively. The scopularides do not belong to any existing group of natural cyclodepsipeptides. Scopularide A und B showed similar inhibitory effects. Both did not inhibit Gram-negative bacteria and showed weak inhibition of Gram-positive bacteria. They significantly inhibited growth of several tumor cell lines, including pancreatic and colon tumor cells. Recently, the genome of *Scopulariopsis brevicaulis* was sequenced.





Scopularide A (1) and B (2)

***Scopulariopsis brevicaulis*, the producer of the cyclodepsipeptides scopularide A (1) and B (2), being active against tumor cell lines.**

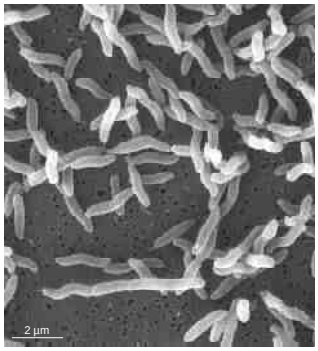
Yu, Z., Lang, G., Kajahn, I., Schmaljohann, R. & Imhoff J.F.: Scopularides A and B, cyclodepsipeptides from a marine sponge-derived fungus *Scopulariopsis brevicaulis*. J. Nat. Prod. 71, 1052-1054 (2008).

Patents: DE10200800097 (2009), EP2229401 (2010)

Kiloniellales, a New Order of Alphaproteobacteria was Isolated from a Brown Alga

Among antibiotically active colonies obtained from the marine macroalga *Saccharina latissima* (formerly *Laminaria saccharina*) a new bacterium (strain LD81), was isolated. This bacterium has a unique phylogenetic position, not fitting any of the known families of the Alphaproteobacteria. The 16S rRNA gene sequence revealed a distant relationship to species of several orders of the Alphaproteobacteria with less than 90% sequence similarity. The new bacterium has a low G+C content of the DNA (51.1%) and due to its distant phylogenetic position to all other Alphaproteobacteria is considered as type strain of the new species and genus *Kiloniella laminariae*, representing the type of the new family Kiloniellaceae and new order Kiloniellales. The bacterium is a mesophilic, typical marine bacterium. It is a chemoheterotrophic aerobic bacterium with the potential of denitrification. Growth optima are at 25 °C, pH 5.5 and 3 % NaCl.

Due to their distant relationship to *Kiloniella*, species of *Terasakiella* and *Thalassospira* are not considered members of the Kiloniellaceae family. They may be included into the order Kiloniellales as separate families.

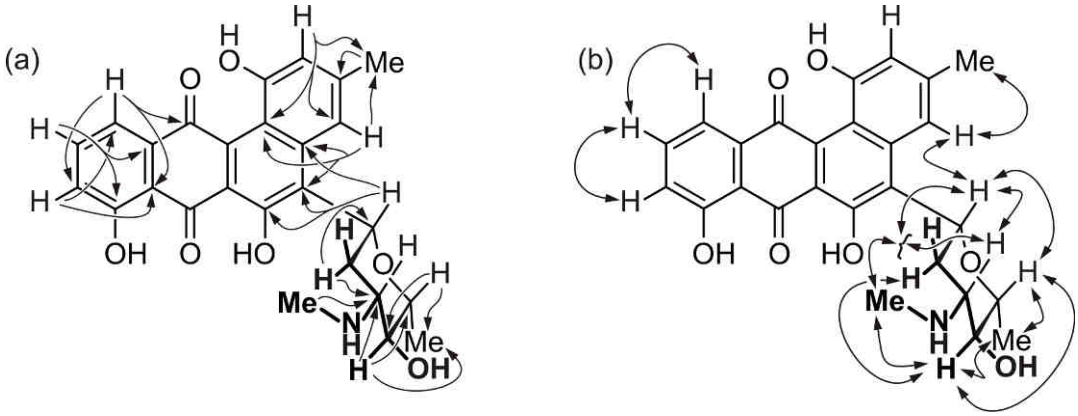


The team involved in establishing *Kiloniella* as a new taxon (right) and microscopic picture of cells of the bacterium (left).

Wiese, J., Thiel, V., Gärtner, A., Schmaljohann, R. & Imhoff, J.F.: *Kiloniella laminariae* gen. nov., sp. nov., a new alphaproteobacterium from the marine macroalga *Laminaria saccharina*. Int. J. Syst. Evol. Microbiol. 59, 350-356 (2009).

Mayamycin, a Potent Antitumor Substance

During a systematic study of Actinobacteria isolated from marine habitats with regard to their potential to produce biologically active natural products, we isolated a *Streptomyces* strain HB202 from the marine sponge *Halichondria panicea*. This study included the selection of promising producers based on bioassay-guided analyses and the detection of genes encoding for the biosynthesis of secondary metabolites. Due to its ability to produce aromatic polyketides as indicated by genetic analyses demonstrating the presence of a type II polyketide synthase and its profound antibiotic activity the strain was selected for further detailed studies. A new benzanthracene derivative was identified in the *Streptomyces* and called mayamycin. The production of mayamycin was induced by variation of the culture conditions. The chemical structure was elucidated by HPLC-DAD/MS and NMR spectroscopy. Mayamycin exhibited potent cytotoxic activity against eight human cancer cell lines and showed activity against several bacteria including antibiotic-resistant strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA).



2D NMR correlations of mayamycin relevant for the structure elucidation (a) HMBC couplings; (b) NOESY correlations.

Schneemann, I., Kajahn, I., Ohlendorf, B., Zinecker, H., Erhard, A., Nagel, K., Wiese, J. & Imhoff, J.F.: Mayamycin, a cytotoxic polyketide from a *Streptomyces* strain isolated from the marine sponge *Halichondria panicea*. J. Nat. Products 73, 1309-1312 (2010).

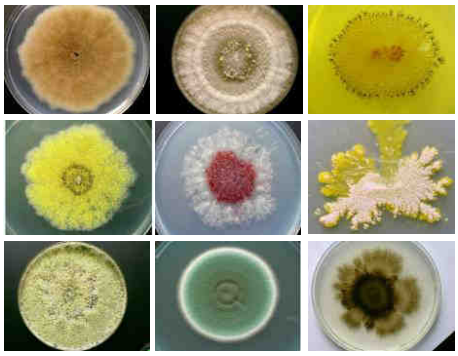
Patents: DE102010006245 (2011), WO/2011/091778 (2011)

A High Diversity of Marine Fungi is Harboured by *Tethya aurantium*

The marine sponge *Tethya aurantium* was found to be a valuable source of secondary metabolite producing fungi. Fungi isolated from *Tethya aurantium* were isolated and identified both by morphological criteria and phylogenetic analysis based on internal transcribed spacer (ITS) regions and were evaluated with regard to their secondary metabolite profiles. More than 200 isolates were obtained, part of these (81 isolates) were characterised. They belong to 21 different genera. Some of these were quite common, such as *Acremonium, Aspergillus, Fusarium, Penicillium, Phoma, and Trichoderma*, while others have rarely been reported from sponges. These include representatives of *Botryosphaeria, Epicoccum, Parasphaeosphaeria*, and *Tritirachium*. Members affiliated to the genera *Bartalinia* and *Volutella* as well as a presumably new *Phoma* species were not previously isolated from sponges. On the basis of their classification, strains were selected for analysis of their natural products.

In addition to a variety of known substances, several new natural products were found. The new cyclodepsipeptides scopularide A and B were produced by a *Scopulariopsis brevicaulis* and these peptides and their activities have been patented because of their antiproliferative activities against several tumor cell lines,

The new cillifuranone is another natural product produced by a fungus (*Penicillium chrysogenum* strain LF066) isolated from *Tethya aurantium* and additional compounds were detected of which the chemical structures are not yet described. The structure of cillifuranone was elucidated based on 1D and 2D NMR analysis and turned out to be a previously postulated intermediate in sorbifuranone biosynthesis. The application of alternative cultivation methods, which have not been used so far, are expected to further increase the spectrum of produced metabolites of our isolates obtained from *T. aurantium*.



More than 200 strains of fungi were isolated from *T. aurantium* and identified. Secondary metabolites of less than half of the strain were studied and revealed >40 new and >40 known compounds so far identified.

Wiese, J., Ohlendorf, B., Blümel, M., Schmaljohann, R. & Imhoff, J.F.: Phylogenetic identification of fungi isolated from the marine sponge *Tethya aurantium* and identification of their secondary metabolites. Mar. Drugs 9, 561-585 (2011).

Genetic Approaches to Detect Pathways for Natural Product Biosynthesis

Genetic approaches for the detection of secondary metabolite pathways are promising tools for the selection of biosynthetically talented microorganisms. So far, main targets in this respect were genes encoding for polyketide synthases (PKSs) or non-ribosomal peptide synthetases (NRPSs), which are involved in two prominent biosynthetic pathways for natural products. By focusing on polyketides and non-ribosomal peptides other interesting compound classes such as phenazines have been neglected so far. Phenazines turned out to be good drug candidates and therefore are promising secondary metabolites. They are heterocyclic, nitrogenous compounds that are substituted at different sites of the core ring system and therefore display a wide range of structural derivatives and biological activities. More than 100 biologically active (antibacterial, antifungal, antiviral, antitumor) phenazines from natural origin are known to date, synthesized mainly by *Pseudomonas* and *Streptomyces* species. A fast and efficient approach was established to identify bacteria possessing the potential to biosynthesize phenazines. Sequences of phzE genes, which codes for one of the enzymes of the phenazine biosynthetic pathway, were used to design one universal primer system and to analyse the ability of bacteria to produce phenazines.

By the investigation of representatives of *Actinobacteria*, which were isolated from the marine sponge *Halichondria panicea* collected from the Baltic Sea (Germany), it has been demonstrated, that the presence of PKS and NRPS genes is a good indicator for the selection of strains to isolate new natural products. For the first time, a comprehensive investigation was performed with regard to phylogenetic strain identification, secondary metabolite profiling, bioactivity determination, and genetic exploration of biosynthetic genes, especially concerning the relationships of the abundance of biosynthesis gene fragments to the number and diversity of produced secondary metabolites. All strains were phylogenetically identified by 16S rRNA gene sequence analyses and were found to belong to the genera *Actinoalloteichus*, *Micrococcus*, *Micromonospora*, *Nocardiopsis*, and *Streptomyces*. Secondary metabolite profiles of 46 actinobacterial strains were evaluated, 122 different substances were identified, and 88 so far unidentified compounds were detected. The extracts from most of the cultures showed biological activities. In addition, the presence of biosynthesis genes encoding polyketide synthases (PKSs) and/or nonribosomal peptide synthetases (NRPSs) was shown in 30 strains. Strains in which either PKS or NRPS genes were identified produced a significantly higher number of metabolites and exhibited a larger number of unidentified, possibly new metabolites than other strains.

Schneemann, I., Nagel, K., Kajahn, I., Labes, A., Wiese, J., & Imhoff, J.F.: Comprehensive investigation of marine Actinobacteria associated with the sponge *Halichondria panicea*. Appl. Environ. Microbiol. 76, 3702-3714 (2010).

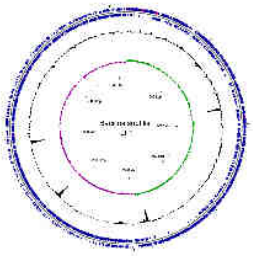
Schneemann, I., Wiese, J., Kunz, A. & Imhoff, J.F.: Genetic approach for the fast discovery of phenazine producing marine Actinobacteria. Mar. Drugs 9, 772-789 (2011).

Genomic Approaches Offer Great Chances in the Discovery of New Natural Products

The KiWiZ has initiated several genome projects to unravel biosynthetic pathways in bacteria and fungi. Genomes of five bacteria have been established, two out of them within a project on antibacterial peptides, and genomes of three marine fungi are currently under investigation within the EU-project “Marine Fungi” coordinated by the KiWiZ in order to unravel their potential for secondary metabolite biosynthesis.

In the following, the first genome sequence of a *Bacillus subtilis* strain gtP20b isolated from the marine environment is discussed as example. *Bacillus subtilis* is a model organism of aerobic spore-forming Gram-positive bacteria and is of great industrial significance as the source of natural antibiotic peptides as well as diverse functional molecules. A subset of candidate genes and gene clusters were identified in the genome sequence, which are potentially involved in production of ribosomal and non-ribosomal antimicrobial peptides, demonstrating the great potential of this strain as a source for novel antimicrobial peptides.

At least 59 genes were found to be involved potentially in bacterial secondary metabolism. These form diverse gene clusters in the contigs sharing a high degree of synteny to those in the released genomes of *B. subtilis* strains like *srf*, *ppt* and *pks* and also a subset of gene clusters, which did not show similarity with those of other *B. subtilis* strains. Hence, they were considered being involved in synthesis of functional molecules specific for strain gtP20b of *B. subtilis* subsp. *spizizenii*. Noticeably, a set of open reading frames (ORFs) was retrieved from antimicrobial peptides (AMPs) databases including subtilisin A (*sboA*), surfactin (*sfp*), beta-lactamase precursor (*penP*) and replicative DNA helicase (*dnaC*) with high sequence similarity. However, there is significant variation at both DNA- and amino acid level of the genes when compared with those of other *B. subtilis* strains, suggesting that the investigated *B. subtilis* strain is a unique source for AMPs.



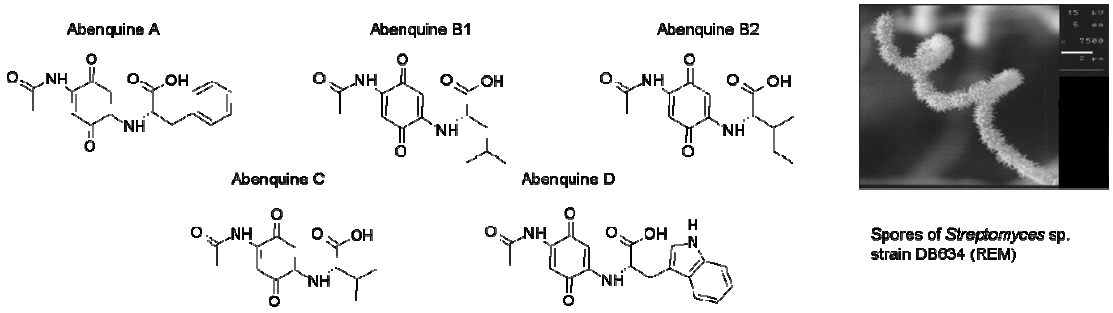
The genome of *Bacillus subtilis subspec. spizizenii* strain gtP20b.

Fan, L., Bo S., Chen, H., Ye, W., Kleinschmidt, K., Baumann, H.I., Imhoff, J.F., Kleine, M. & Cai, D.: Genome sequence of *Bacillus subtilis* subsp. *spizizenii* gtP20b isolated from the Indian Ocean. J. Bacteriol. 193, 1276-1277 (2011).

Directed Biosynthesis Gives Rise to Derivatives of Abenquines

Five new bioactive secondary metabolites, called abenquines were produced by a *Streptomyces* strain DB634 isolated from the Atacama Desert in the Chilean highland. They are composed of an amino acid linked to an N-acetyl-aminobenzoquinone. The chemical structure of abenquines was established by NMR analysis and mass spectrometry. The abenquines are simple benzoquinones substituted with different amino acids via the amino group and are uncommon microbial metabolites. Structurally related compounds which share N-substituted aminobenzoquinones as a structural feature are lepiotaquinone (from *Lepiota americana*) and lilacinone (from *Lactarius lilacinus*), which are found as pigments in fungi. Interestingly, apart from fungi, sponges also produce products emerging from benzoquinones and amino acids.

Abenquines show moderate inhibitory activity against bacteria, dermatophytic fungi and phosphodiesterase type 4b. The amino acid attached to the quinone is relevant to the enzyme inhibitory activity and can be modified by the supplementation of cultivation media with different amino acids. Cultivation experiments and feeding with different amino acids revealed clear preferences for the incorporation of some amino acids.



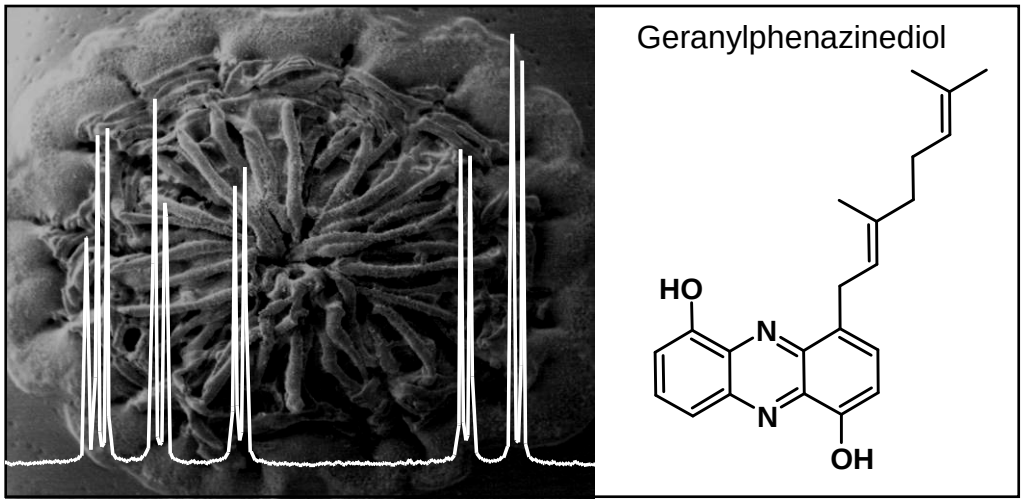
The biosynthesis of different derivatives of abenquines by Streptomyces DB634 depends on the amino acids supplied with the growth medium.

Schulz, D., Beese, P., Ohlendorf, B., Erhardt, A., Zinecker, H., Dorador, C. & Imhoff, J.F.: Abenquines, aminoquinone derivatives produced by *Streptomyces* sp. strain DB634. J. Antibiotics 64, 763-768 (2011).

Acetylcholinesterase Inhibitor Produced from a Marine *Streptomyces*

Acetylcholinesterase (AChE) is an enzyme responsible for the degradation of the transmitter acetylcholine. Inhibitors of this enzyme such as galantamine or rivastigmine enhance the amount of available acetylcholine and thereby improve cholinergic transmission. These compounds are used to alleviate the symptoms of Alzheimer's disease which is associated with degeneration of cholinergic neurons and impaired transmission.

Geranylphenazinediol is a new phenazine natural product, produced by *Streptomyces* sp. strain LB173, which was isolated from a marine sediment. The structure was established by analysis of NMR and MS data. Geranylphenazinediol inhibited the enzyme acetylcholinesterase in the low micromolar range and showed weak antibacterial activity. In order to get a more detailed picture of the activity profile of geranylphenazinediol, its inhibitory potential was compared to that of related structures.



Geranylphenazinediol is an acetylcholinesterase inhibitor produced by a marine *Streptomyces* isolate.

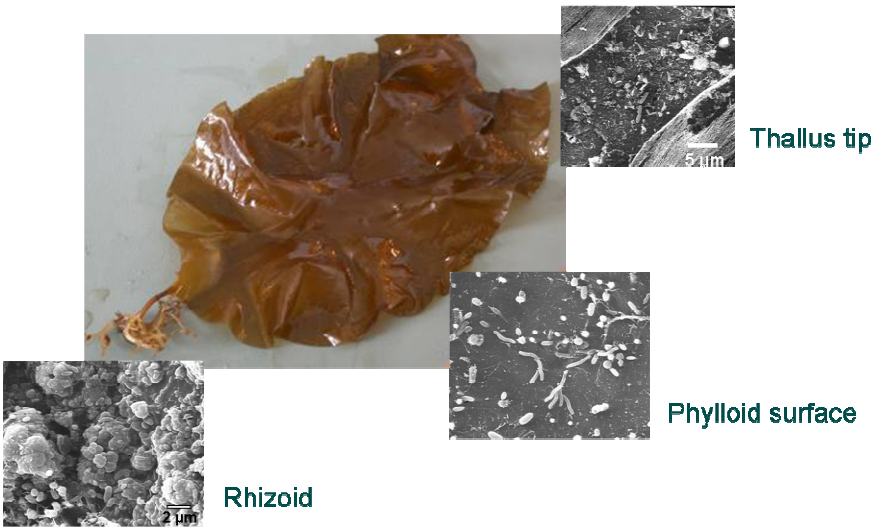
Ohlendorf, B., Schulz, D., Erhard, A., Nagel, N. & Imhoff, J.F.: Geranylphenazinediol, an acetylcholinesterase inhibitor produced by a *Streptomyces* species. J. Nat. Prod. 75, 1400-1404 (2012).

Saccharina latissima-Associated Bacteria are Potent Producers of Antimicrobial Compounds

The bacterial communities of the brown macroalga *Saccharina latissima* (synonym *Laminaria saccharina*) harbour a large number of antimicrobial active bacteria, including several *Pseudomonas* species. Secondary metabolites are proposed to positively affect the survival of their producers. Also the host may benefit from inhibition of competing, degrading and potentially pathogenic surface-colonising microorganisms.

Pseudomonas strains regularly were shown to be associated with the brown macroalga *Saccharina latissima* from the Baltic Sea over several years and were identified as producers of the antimicrobial active compound 2,4-diacetylphloroglucinol. The metabolite profile of the *Pseudomonas* strains comprised monoacetylphloroglucinol (MAPG), 2,4-diacetyl-phloroglucinol (DAPG), pyoluteorin (PLT) and several rhizoxins, which exhibited broad-spectrum antibiotic activities against Gram-positive and Gram-negative bacteria as well as against fungi

Because DAPG, MAPG and PLT are active against *Pseudoalteromonas elyakovii* and *Algicola bacteriolytica*, which are hypothesised to cause disease of Saccharina japonica, we suppose, that through production of these antibiotic compounds the marine pseudomonads may be beneficial for the macroalgal host.



Electron microscopy and genetic evidence demonstrate different colonisation of different parts of the alga *Saccharina latissima* by bacteria.

Nagel, K., Schneemann, I., Kajahn, I., Labes, A., Wiese, J. & Imhoff, J.F. Proposed beneficial effects of 2,4-diacetylphloroglucinol-producing pseudomonads on the marine alga *Saccharina latissima*. AME *in press*

Scientific Cooperations of KiWiZ

The KiWiZ became a strong partner in networks on marine biotechnology in Schleswig-Holstein and northern Germany and is partner for a number of small commercial companies and of numerous scientific research groups on local, national and international scales.

- The KiWiZ is engaged in research collaborations on local, national and international level. The KiWiZ coordinates a EU cooperation project and is partner of a coordination activity in the FP7 of European Community.
- Besides scientific publications and presentations (see chapter The KiWiZ - a platform for marine natural product research), the KiWiZ initiated the colloquium "Marine Natural Products" to enforce communication with German and foreign colleagues.
- A number of visiting scientists were hosted at the KiWiZ and foreign PhD students supervised either in short term visits for education in specific methods or for the full length of the PhD thesis.

Research Projects and Cooperations

Marine biotechnology using small compounds is a key component in national and international interdisciplinary networks in an EU-wide framework. These networks connect the KiWiZ to integrated approaches in this innovative field. These activities form a bridge from environmental marine science to applied marine biotechnological research. They also form a strong link to the large fraction of Helmholtz Centres performing health related research.

National level

Cooperation with universities. Based on the wide methodological expertise of the KiWiZ, different aspects are attractive for cooperation partners. Major aspects of cooperations are related to assays on biological activities of natural products. In this context partners are from natural product chemist laboratories of the universities of Tübingen, Siegen, Berlin, Bonn, and from MPI in Jena. The KiWiZ is continuously extending its own panel of bioassays and in addition uses those of expert partners at the CAU Kiel (UK-SH Kiel) for e.g. antitumoral, antiviral and medicinal important antibacterial assay systems. Increasing importance is gained by the KiWiZ substance library which is requested for use in special screening systems by partner groups, such as the European Screening Port (Hamburg) and the Centre for Infection Research HZI (Braunschweig).

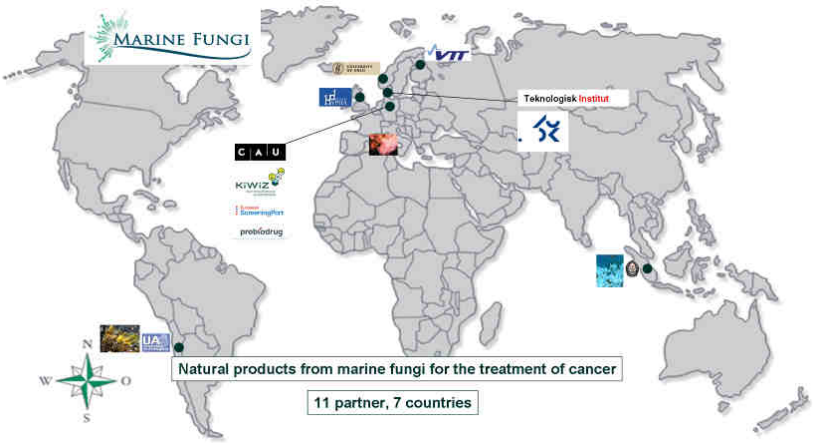
Cluster of Excellence of the University Kiel CAU. The KiWiZ promoted the inclusion of marine natural products as a topic of the Cluster of Excellence "Future Ocean I" and also contributes to the actual phase II. KiWiZ is also partner within the Cluster of Excellence "Inflammation at interfaces".

BIOCATALYSIS2021. The KiWiZ actively promoted the concept and proposal of a cooperative project within the biotechnology cluster BIOCATALYSIS2021. The topic of the project was on antimicrobial peptides from marine bacteria, which is an important group of bioactive compounds. The joint project was funded from 2008-2011 and included the Planton GmbH (Kiel) and the University of Kiel (Prof. Cai, Department of Plant Pathology) as partners.

European framework

At the European level, the KiWiZ cooperates with a variety of partners via bilateral cooperation, acts as coordinator of the project "MARINE FUNGI" within the "Seventh Framework Programme" (FP7) and has applied for a large cooperative project with 20 partners, including 7 industrial partners (highly ranked with 12.5 out of 15 points). It is involved in preparatory activities for the upcoming programme "Horizon 2020".

MARINE FUNGI. The KiWiZ coordinates the EU project MARINE FUNGI aiming to demonstrate the sustainable exploitation of under-utilised marine natural resources for the production of antitumor substances. By providing appropriate culture conditions for marine fungi, the efficient production of marine natural products in the laboratory and the scale up in a sustainable process without harm to the natural environment is achieved. The therapeutic focus of MARINE FUNGI is the development of novel anti-cancer compounds. The project will carry out the characterisation of these compounds to the stage of *in vivo* proof of concept ready to enter further drug development in order to valorise the results of the project. It will further promote natural product biosynthesis of three selected fungi by genome sequencing and genetic methods to improve our knowledge on biosynthetic properties of the fungi. A group of eleven institutions from seven different countries including four companies has joined forces to set up a consortium of experts to cooperatively conduct the ambitious project, which is funded by the European Commission under the "Seventh Framework Programme" (FP7).



MARINE FUNGI partners from Europe, Indonesia and Chile working on the biology of marine fungi for the discovery and development of new anti-cancer drugs.

International level

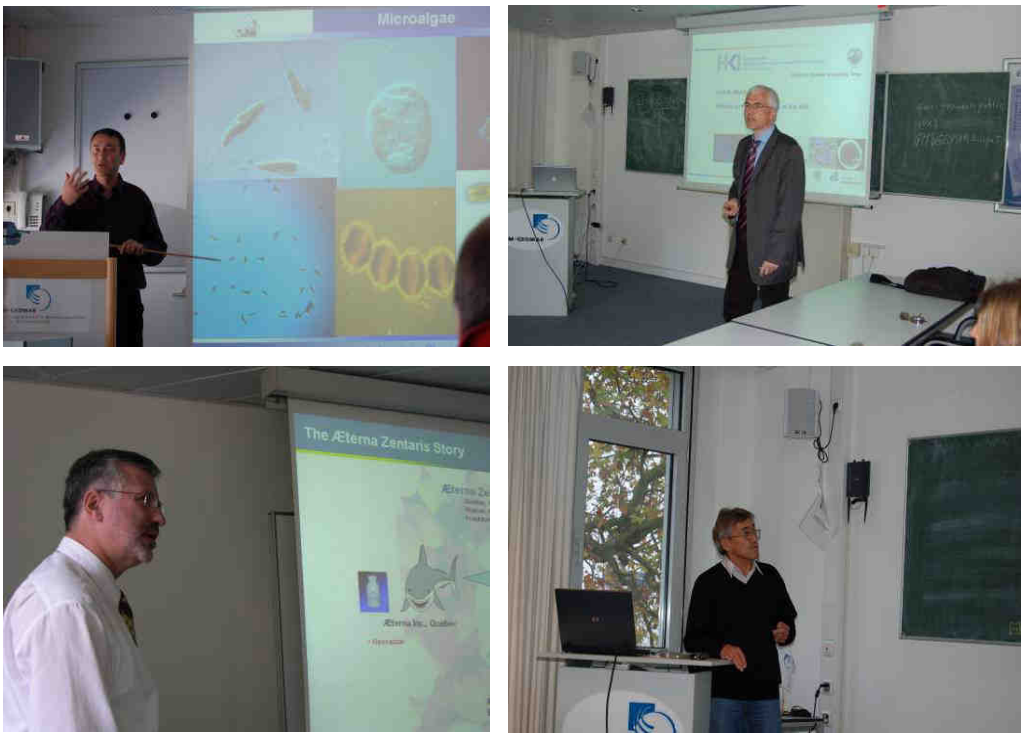
Major ongoing international cooperations include partners from

- the Facultad de Recursos del Mar (Universidad de Antofagasta, Chile) covering aspects of diversity and secondary metabolites of selected bacterial groups (including fungi) from extreme habitats and from Chilean algal forests
- the Diponegoro University (Semarang, Indonesia) with a project on natural products from marine fungi
- the University Kunming (China) with an intensive exchange of strains and knowledge established during the past years, where currently the capacities of chemical analyses of KiWiZ are major aspects of interest by the Chinese partners.

Signing contract of coperation with Prof. Cheng-Lin Jiang from the National Engineering Center for Research of Microbial Pharmaceuticals, Yunnan University, Kunming (China) (top left), celebrating this with a formal dinner (lower left), group photo with the research group of the Kunming institute (upper right). Marine natural products were topic on the World Ocean Congress in Manado, group photo (lower right) together with our former guest researcher and project partner Prof. Ocky Karna Radjasa from the Department of Marine Science of Diponegoro University in Semarang (Indonesia).

Scientific Colloquium ”Marine Natural Products”

In order to enforce communication and cooperation with other scientists and scientific institutions as well as industrial companies a scientific colloquium was established with invited speakers from science and industry. The lectures gave a broad spectrum of specific aspects of natural product research and included aspects from the industrial perspective as well.



As representatives four guest speakers are shown in action : Prof. Dr. Jean-Paul Cadoret from IFREMER in Nantes, France (upper left), Prof. Dr. Axel Brakhage from the HKI in Jena (upper right), Dr. Eckhard Günther from Drug Discovery and Preclinical Development of Æterna Zentaris in Frankfurt (lower left) and Prof. Dr. Hans-Peter Fiedler from the University in Tübingen (lower right).

Invited speakers of the colloquium ”Marine natural products”

Dr. Joachim Rheinheimer, BASF, 18.3.2008: “Naturstoffe in der Pflanzenschutzforschung. Arbeitsweise und das Vorgehen bei der Bearbeitung von Leitstrukturen aus der Natur.“

Prof. Dr. Roderich D. Süssmuth, Technische Universität Berlin, 08.05.2008: “Vancomycin, Abyssomicin, Proximicin - Struktur, Biosynthese und Wirkmechanismus von alten und neuen Naturstoffen“

Prof. Dr. Jean-Paul Cadoret, IFREMER, Laboratoire de Physiologie et Biotechnologie des Algues, Nantes, Frankreich, 9.5.2008: “Microalgae: Biotechnology and applications“

Dr. Ute Dechert, Senior Scientist Analytics / Controlling R&D, BRAIN Aktiengesellschaft Zwingenberg, 15.05.2008: “BRAIN Philosophie“

Dr. Eckhard Günther, Vice President, Discovery and Preclinical Development, Æterna Zentaris GmbH / Frankfurt / M., 29.05.2008: "Naturstoffe als Leads - Enttäuschte Hoffnungen? Das Beispiel des BioTech-Unternehmens AEterna Zentaris"

Prof. Dr. Lutz Heide, Pharmazeutische Biologie, Universität Tübingen, 20.06.2008: "Genetische Manipulation von Naturstoffproduzenten: Neue Aminocoumarin-Antibiotika durch Metabolic Engineering und Mutasynthese"

Prof. Dr. Christian Hertweck, Leibniz Institute for Natural Product Research and Infection Biology – Hans-Knöll-Institute (HKI), Jena, 15.07.2008: "Natural product assembly lines and their role in microbial interactions"

Prof. Dr. Axel Zeeck, Institut für Organische und Biomolekulare Chemie - Abteilung Biomolekulare Chemie – Göttingen, 17.10.2008: "Wie findet man neue mikrobielle Naturstoffe? – Rückblick und Perspektiven"

Prof. Dr. Hans-Peter Fiedler, Universität Tübingen, Mikrobiologisches Institut, 7.11.2008:

"Albidopyrone: Neue Wirkstoffe aus marinen und terrestrischen Actinomyceten"

Prof. Dr. Axel Brakhage, Leibniz Institute for Natural Product Research and Infection Biology – Hans-Knöll-Institute (HKI), Jena, 4.6.2009: "Natural Product Discovery at the Leibniz-Institute for Natural Product"

Prof. Dr. Rüdiger Schulz, Botanisches Institut CAU Kiel, 16.7.2009: "Mikroalgen-Screening: Optimierung der biotechnologischen und bioenergetischen Nutzung"

Prof. Dr. Frank Kempken, Botanisches Institut CAU Kiel, 1.10.2009: "Filamentous fungi as model systems in molecular genetics"

Prof. Dr. Fernando De la Calle, PharmaMar, Madrid, Spanien, 2.7.2010: "Marine Biodiversity and Biotechnology applied to human health. The experience of PharmaMar"

Prof. Dr. Christian Peifer, Pharmazeutische Chemie CAU Kiel, 26.1.2012: "Structure-based design of kinase inhibitors"

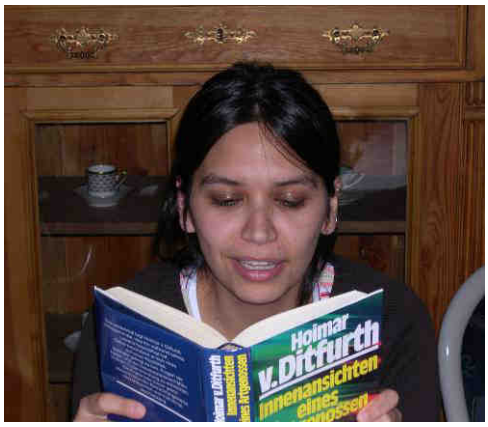
Dr. Philip Gribbon, European Screening Port, Hamburg, 28.6.2012: "Academic drug discovery in Europe"

Dr. Fiona Chan, Xention Ltd., Great Britain, 29.6.2012: "Drug development in a nutshell"

Visiting Scientists

The KiWiZ is an attractive research centre for foreign scientists as demonstrated by a great number of requests and applications to work as guest scientists in our laboratories. The requests come from many countries all over the world.

Research fellows with financial support which worked as guests in KiWiZ laboratories came from Bulgaria (Dr. Maya Mitova, Humboldt fellow), Indonesia (Prof. Dr. Ocky Karna Radjasa, Humboldt fellow), China (Dr. Suping Yang (photo right), Prof. Dr. Chen-Lin Jiang (photo middle) and Prof. Dr. Yu Zhiguo (photo right), Egypt (Dr. Ahmed Mohamed El-Bondkly) and Chile (Dr. Cristina Dorador, DAAD, photo left). Currently, Martha Hengst Lopez (Universidad de Antofagasta, Chile) is visiting KiWiZ for research work. In Oktober 2012, Prof. Bin Wu from Zhejiang University of China started for a year at KiWiZ for to perform natural product chemical studies.




Foreign PhD Students

The application rate of PhD students with special emphasis on the research work of KiWiZ is overwhelming and a strong selection is necessary to select those that can be supervised in the KiWiZ during their PhD studies. Students that came for special short term training were Ju Hyoung Lim from Korea and Sarijito from Indonesia. Students that finished her complete PhD thesis in Kiel were Yi Jiang from China and Franz Goecke from Chile. Currently, Sun Min from China and Mien Thi Pham from Vietnam are performing their PhD studies in the KiWiZ.

Education

The KiWiZ has a prominent position in education on marine biotechnology, although a formal curriculum is not offered. Marine natural product research and marine biotechnology attract students from whole Germany. The KiWiZ is naturally involved in the curriculum of Biological Oceanography through engagement of the Marine Microbiology Research Unit and offers special courses on “Microbial interactions” in this frame. In addition, it offers practical courses in marine biotechnology and supervises students in their work during bachelor and master theses (in the past also for diploma theses). More than 40 students were supervised during the past years in different stages of their education. In addition, a number of eight PhD students completed the thesis at the KiWiZ (see list below) and another eight PhD theses are ongoing.

A major fraction of the students is coming from various German and Swiss universities (Aachen, Berlin, Bonn-Rhein-Sieg, Dortmund, Düsseldorf, Duisburg, Gelsenkirchen, Greifswald, Flensburg, Münster, Muttenz, Regensburg, Rostock, Ulm). Particular close cooperations in education exist with the Elly-Heuss-Knapp-Schule in Neumünster in education of technicians in biotechnology and to the University of Applied Sciences Flensburg in supervision of practical studies of biotechnology engineers.

PhD Dissertations Completed

Vera Thiel: Sponge-associated bacteria: specificity, diversity and antimicrobial potential (2006).

Yi Jiang: Systematic research on Actinomycetes selected according to biological activities (2009).

Andrea Gärtner: Isolation and characterization of bacteria from the deep-sea and their potential to produce bioactive natural products (2011).

Imke Schneemann: Nachweis von Biosynthesegenen des bakteriellen Sekundärstoffwechsels sowie Isolierung und Strukturaufklärung von Naturstoffen aus ausgewählten Actinomyceten (2011).

Herwig Heindl: Antimicrobially active microorganisms associated with marine bryozoans (2011).

Franz Goecke: Association between microbes and macroalgae: host, epiphyte and environmental effects (2011).

Tim Staufenberger: Chitinases in the tree of life. Ecological, kinetic and structural studies of archaeal and marine bacterial chitinases (2012).

Katrin Kleinschmidt: Isolierung und Charakterisierung von Bakterien aus Meeressedimenten und ihr Potential zur Produktion von antimikrobiellen Peptiden und Polyketiden (2012).

Summer School on “Marine Biotechnology and Natural Products”

The summer school on “Marine Biotechnology and Natural Products” is offered to selected Swiss students from the School of Life Sciences at the University for Applied Sciences Northwestern Switzerland (FHNW) in Muttenz/Basel since 2009. It is an optional module in the frame of studies on molecular life sciences with the title “Research in the context of knowledge and application”. This summer school is a highly appreciated choice of the Swiss students and gives a comprehensive introduction to the marine natural product research from the sampling on board of a research vessel to isolation and identification of the bacteria, to chemical extraction and purification and to testing of bioactivities within the frame of the possibilities available at the KiWiZ Research Laboratories.

Contacts with our colleagues from the Swiss university also have initiated a research collaboration in which our substances are *in silico* characterised for structure activity relationship evaluation and rational structure based design.

Students and supervisors of the summer school Marine Biotechnology 2009 (left) and participants of the technology summer school in front of the venue Wissenschaftzentrum Kiel (right).

Summer School on “Methods in Biotechnology”

An international summer school was organised with 35 participants from universities, companies and research institutions from China, Brazil, Spain, Lithuania, Vietnam, Belgium and Germany in 2011 together with the Helmut-Schmidt-University Hamburg and the cluster BIOCATALYSIS2021. Contributions from industry were presented by the companies BioLogics Richter-Helm, GE Healthcare, Knauer, BioSilta and Hamilton. The graduate students contributed to the topic with oral presentations and posters from their current research. Lively discussions complemented the lectures.

Awards

Several awards have been given to scientists from the KiWiZ and to the KiWiZ as an innovative research facility. In 2009, the KiWiZ has been awarded as one of the “Ort im Land der Ideen” by the German Federal President for its outstanding concept in research and development of marine natural products.

The KiWiZ receives certificate and award and celebrates this by opening the doors and presenting its laboratories to the public.

In 2007 Prof. Johannes F. Imhoff received the “Paul J. Scheuer – Preis” for outstanding scientific work in natural product research together with Prof. Dr. Dr. h.c. Gerd Bringmann and Prof. Dr. Werner E.G. Müller, awarded by the Akademie gemeinnütziger Wissenschaften zu Erfurt.

In 2011 Dr. Jutta Wiese received the IFM-GEOMAR publication award for outstanding scientific publication efforts.

Work presented and published by KiWiZ scientists on congresses has been awarded several times for presented posters on scientific meetings.

KiWiZ as a Thriving Force for Networking and Promotion of Marine Biotechnology

During the past years, the KiWiZ has established numerous contacts, bilateral agreements, and networks of partners in academia and industry on regional, national, European and international level. Many of these activities aim to strengthen the role of marine biotechnology and its visibility. In this framework, in particular innovative products of small companies in Schleswig-Holstein were supported by knowledge and know-how. Networking activities are supported by WTSH and NORGENTA.

Networks for Marine Biotechnology

Networks with research institutions and commercial enterprises are established to promote natural product research, to transfer research results into commercial applications and to support small companies in developing products for the market.

Northern Network

The "Northern Network of Marine Biotechnology" is a joint activity of research groups and companies in northern Germany to strengthen the research capabilities and promoting product development of marine resources. Members are

- research teams and institutions dedicated to research on marine natural compounds
- companies with products from marine natural compounds
- organisations that support blue biotechnology in the region.

Submariner: Sustainable Uses of Baltic Marine Resources

The Baltic Sea Region (BSR) faces enormous challenges including growing transport, new installations, fishery declines, severe marine pollution, excessive nutrient input, and the effects of climate change. But novel technologies and growing knowledge also provide opportunities for new uses of marine ecosystems, which should not only be valued for their commercial appeal but for their potentially significant contribution to solving its environmental problems. Submariner paves the road for furthering those environmentally friendly as well as economically appealing innovative uses within the BSR, thus contributing towards its aim to become a model region for sustainable management of the sea. The KiWiZ participates in this process and coordinates the evaluation of aspects of blue biotechnology. The project is funded by the Baltic Sea Region Programme 2007-2013.

Biotech Center Kiel

The KiWiZ joined with two biotechnology companies (Planton GmbH and Proteo AG) under the umbrella of the Kiel Biotech Center to combine expertise in biotechnology and strengthen this field in Kiel.

Science Meets Industry: Support of SMEs and Local Structures

As a network node between research and application, the KiWiZ expanded its contacts with the economy. These activities include pure analytical work but also application-oriented research projects, which aim to develop or improve products or production methods. In some cases the cooperation has merged into joint product development. Most companies are located in Schleswig-Holstein and northern Germany, but requests come and projects exist with companies from other parts of Germany and from other European countries. A current EU research project and preparatory work for another proposal greatly stimulated contact with European biotechnological companies.

The KiWiZ is research partner in the network of competence for food industry Schleswig-Holstein and offers service and support for product development to the participating companies.

Blue Biotechnology Cooperation Event

Within the scope of the SUBMARINER project, the KiWiZ and Norgenta North German Life Science Agency GmbH organised and hosted the international Blue Biotechnology Cooperation Event “New Strategies and Future Perspectives”. It took place in Kiel on 9 and 10 May 2012.

Blue Biotech Cooperation event. More than 150 representatives of research institutions, private companies, politics and public institutions in the field of blue biotechnology participated in this event which offered a platform for networking and cooperation.

Competence workshop "Development of biotechnological processes and product preparation”

In cooperation with BIOCATALYSIS2021 and Prof. Dr.-Ing. Bernd Niemeyer (Helmut-Schmidt University Hamburg), a workshop on "Development of biotechnological processes and product processing" was organised in 2010 in Lübeck. The focus of the event was an intensified networking of academic research and industrial application. Aspects of technical knowledge and transfer of biotechnological processes from the laboratory to industrial scale comprehensive were treated. Further topics were strategical linkages between various technological disciplines and a thorough understanding of knowledge on metabolic processes of microorganisms. Both the upscaling and downstream processing were additional tasks.

From science to industry

The KiWiZ was established with the specific goal to generate and transfer knowledge and products from science to industry. In the central focus of such activities were substances isolated from marine microorganisms and their biological activities with potential use in medicine and cosmetics. Such products are candidates for long term developmental strategies. In short term, scientific knowledge and methodological capabilities are major aspects of contacts to industry. In particular local companies request support in analytical problems or in process development. The wide range of analytical aspects available at the KiWiZ is asked for and includes microbiological and chemical analyses as well as determination of biological activity profiles of substances and extracts. Also individual substances available at the KiWiZ and the complete library of natural products are requested for different purposes. In addition, the KiWiZ has initiated the development of its own products to be transferred to the market by commercial partners. The commercial aspects are promoted by the small associated enterprise MicrobiMaris Biotec GmbH. Partnerships are sought preferably with small and medium-sized companies but also with larger corporations.

Presentations to Stakeholders

KiWiZ presented its laboratories to the public and to the political community on a number of occasions. Examples are presented: The major of Kiel Angelika Volquartz was patron for the BIOTECH CENTER Kiel and honorary speaker at the celebration of awarding KiWiZ the "Ort im Land der Ideen" (top left). The director for North Sea and Baltic Sea affairs in the general direction Mare in Brussels Haitze Siemers together with Uwe Döring visited KiWiZ (top right). Prime minister of Kiel government Peter H. Carstensen and the parliamentary state secretary and coordinator of maritime economy of the German federal government Dagmar G. Wöhrl visited KiWiZ and were informed about ongoing work (middle). State secretary of the ministry for „ Ministry of Economic Affairs, Employment, Transport and Technology" Cordelia Andreßen visited KiWiZ (bottom).

Presentations to the Wider Public

In order to promote aspects of marine biotechnology and in particular of marine natural products and their potential for drug development into the public, the KiWiZ has presented special topics of these aspects in several public exhibitions (see list in appendix). For this purpose specific media were developed to translate scientific issues for the wider public. These include a corporate video „Medizin aus dem Meer: Das Kieler Wirkstoff-Zentrum KiWiZ“, a touch screen and show and various exhibition items.

The KiWiZ was presented twice at Biotechnica fair, a good possibility to interact with both, scientific and industrial partners. Within the scientific programme of Analytica and Achema, KiWiZ topics were presented. Additionally, the KiWiZ was present at specific fairs, such as Beauty (cosmetic sector) and the local Husum Innovation Messe in 2012.

Exhibitions on board of the exhibition ship MS Wissenschaft “Jenny” (left) and at the fair Biotechnica 2008 in Hannover (right).

Public Presence

The KiWiZ was very active in promoting blue biotechnology but as well was topic or information source in newspapers, radio, television and press releases. It presents its activities in a flyer, project web sites (www.kiwiz.org, www.marinefungi.eu), as well as in interviews and public lectures. An overview on these activities is given in the appendix.

Resume and Future Perspectives

Due to the facts that most big pharma companies have reduced significantly their research activities, that the pipelines of new drugs for the market are fading and that a strong demand is recognised for new substances to fill these pipelines, it is crucial that research institutions intensify the search for new bioactive compounds. The availability of new candidates for the drug pipelines is a recognised serious bottleneck for the development of new drugs. As nature is the master designer for chemical compounds with a high variety of structures and a large number of biological activities with experience of several billion years, natural products and derivatives thereof were the primary source for drug development. Hit rates for bioactive compounds are much larger in marine organisms than in other sources and therefore marine life is the preferred source for the search of new drugs. It is the high structural novelty coupled with new modes of biological activity that continue to make the study of marine natural products a rewarding venture (Grabowski et al., 2008). **Opinions from leaders in the field of marine natural products all agree that the potential of marine pharmaceuticals significantly will contribute to the pharmacopoeia**.

In particular the microbiological focus of the KiWiZ offers great chances for the future of marine natural product research and of marine biotechnology. The almost unlimited microbial diversity of the ocean itself represents a huge potential for biotechnological exploitation, including marine natural products. No matter whether culture-dependent or culture-independent approaches are used, current and future technologies will multiply the possibilities of exploring the potential of producing natural products by marine bacteria and fungi. The potential of pure cultures of marine microbes will be much better explored by applying genetic screening methods, which have been developed during the past years at the KiWiZ and are currently applied, as well as by applying genomic approaches. The analyses of genome sequences already have shown that only a small fraction of the genetic potential is phenotypically expressed. Hence, the application of genomic approaches will enhance the search for new natural products.

The research strategies of the KiWiZ together with the established research platform and the valuable biological and genetic resources available, as outlined in this brochure, are excellent conditions to successfully work and compete in this field.

This in mind, it can be expected that the KiWiZ will significantly contribute to the marine natural product development in the coming years, **if supported adequately to maintain basic structures and methodological know-how**.

Structural Opportunities and Challenges

Marine biotechnology with all its facets relevant to application represents an enormous economic potential for Europe. The CSA „MarineBiotech“ (coordination support activity, an instrument of EU) will advance progress in this field towards the vision of a

European Research Area (ERA) and promote and position marine biotechnology as a sector which can deliver ‘smart, sustainable and inclusive growth’, a core objective of the Europe 2020 Strategy. A possible resulting ERAnet is in line with all KiWiZ activities.

In general **the research strategy of the KiWiZ** is in accord with recognised demands by science and research priorities defined by political levels from the European Commission to the government of Schleswig-Holstein. This includes participation in current activities of “EU Openscreen”, an initiative for establishment of an European infrastructure of open screening platforms for chemical biology.

Expected Outcome

Depending on the future focus of the KiWiZ, we expect significant progress in our understanding of biology and chemistry of small bioactive molecules, their role in interactions between marine micro- and macroorganisms and in shaping microbial communities and even modifying ecosystem structure and biogeochemical fluxes.

The huge potential of the marine microbial world to produce biological active metabolites and the excellent resources of microorganisms with their genetic and physiological potential available at the KiWiZ will give rise to the discovery of an increasing number of new chemical compounds. By systematic investigations of these resources, new lead structures with bioactivities of relevance for application in human diseases, in plant protection, in marine diseases and possibly other fields of application will be identified and promoted to products.

The continued exploration of genomes from marine bacteria and fungi will lead to a significant broadening of our general understanding of marine biodiversity and in particular on evolutionary aspects of natural product biosynthesis.

Considering that

- the role of small bioactive molecules in biological interactions in marine organisms is almost unknown,
- the marine microorganisms are a huge reservoir of bioactive substance producers that is almost untouched,
- an increasing pressure will be on the search and identification of new natural products for pharmaceutical use,
- KiWiZ has well equipped laboratories and excellent know-how,
- KiWiZ has invaluable genetic and organismic resources and access to a wide range oceanic habitats,

it is reasonable to assume that KiWiZ is in an excellent position to meet future challenges of marine natural product research for the coming decades if not the century.

The established KiWiZ research platform is both, a basis for a comprehensive and sustainable exploitation of natural compounds from marine microorganisms and a great structural opportunity for leading an exciting field of marine sciences.

References of this Report

Citations of our own publications are found under Scientific Publications in the appendix below.

Børresen T, Boyen C Dobson A, Höfle M, Ianora A, Jaspars M, Kijjoa A, Olafsen J, Querellou J, Rigos G, Wijffels R. Marine Biotechnology: A New Vision and Strategy for Europe. Marine Board-ESF Position Paper 15. 2010

Cragg GM, Grothaus PG, Newman DJ (2009) Impact of natural products on developing new anti-cancer agents. Chem Rev 109:3012-3043

DeLong EF (2007) Modern microbial seascapes. Forward. Nat Rev Microbiol 5:755-757

DeLong EF, Preston CM, Mincer T, Rich V, Hallam SJ, Frigaard NU, Martinez A, Sullivan MB, Edwards R, Brito BR, Chisholm SW, Karl DM (2006) Community genomics among stratified microbial assemblages in the ocean's interior. Science 311:496-503

Gerwick WH, Moore BS (2012) Lessons from the past and charting the future of marine Natural products drug discovery and chemical biology. Chem Biol 19:85-98

Grabowski K, Baringhaus KH, Schneider G (2008) Scaffold diversity of natural products: inspiration for combinatorial library design. Nat Prod Rep 25:892-904

Kube, N, Waller U. Marine Naturstoffe in der Blauen Biotechnologie Stand und Perspektiven. 2003. Ed: Technologiestiftung Schleswig-Holstein.

Martin SM, Kau DA, Wrigley SK (2005) Scale-up of natural products isolation. *In* Natural Products Isolation 2nd Edition, Eds. Sarker SD, Latif Z, Gray AI. Humana Press, p439-461

Mayer AM, Glaser KB, Cuevas C, Jacobs RS, Kem W, Little RD, McIntosh JM, Newman DJ, Potts BC, Shuster DE (2010) The odyssey of marine pharmaceuticals: a current pipeline perspective. Trends Pharmacol Sci 31:255-265

Molinski T (2009) Marine natural products. Clin Adv Hematol Oncol 7:383-385

Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. J Nat Prod 70:461-477

Pettit GR, Herald CL, Doubek DL, Herald DL, Arnold E, Clardy J (1982) Isolation and structure of bryostatin-1. J Am Chem Soc 104:6846-6848

Rath CM, Janto B, Earl J, Ahmed A, Hu FZ, Hiller L, Dahlgren M, Kreft R, Yu F, Wolff JJ (2011) Meta-omic characterization of the marine invertebrate microbial consortium that produces the chemotherapeutic natural product ET-743. ACS Chem Biol 6:1244-1256

Simon C, Daniel R (2009) Achievements and new knowledge unraveled by metagenomic approaches. Appl Microbiol Biotechnol 85:265-276

Simon C, Daniel R (2010) Metagenomic analyses: past and future trends. Appl Environ Microbiol 77:1153–1161

Sudek S, Lopanik NB, Waggoner LE, Hildebrand M, Anderson C, Liu H, Patel A, Sherman DH, Haygood MG (2007) Identification of the putative bryostatin polyketide synthase gene cluster from "*Candidatus* Endobugula sertula", the uncultivated microbial symbiont of the marine bryozoan *Bugula neritina*. J Nat Prod 70:67-74

Appendix

Scientific Publications KiWiZ 2006 – 2012

Peer-reviewed scientific journals

1. Jiang, Y., Tang, S.K., Xu, L.H., Imhoff, J.F., Liu, Z.H., & Jiang, C.L.: Analysis of secondary structure of the family Yaniaceae. Microbiol. 33, 176-179 (2006).
2. Thiel, V., Neulinger, S.C., Staufenberger, T., Schmaljohann, R. & Imhoff, J.F.: Spatial distribution of sponge-associated bacteria in the Mediterranean sponge *Tethya aurantium.* FEMS Microbiol. Ecol. 59, 47-63 (2007).
3. Bringmann, G., Gulder, T.A.M., Lang, G., Schmitt, S., Stöhr, R., Wiese, J., Nagel, K. & Imhoff, J.F.: Large scale biotechnological production of the antileukemic marine natural product sorbicillactone A. Mar. Drugs 5, 23-30 (2007).
4. Radjasa, O.K., Salasia, S.I.O., Sabdono, A., Wiese, J., Imhoff, J.F., Lämmler, C. & Risk, M.J.: Antibacterial activity of marine bacterium *Pseudomonas* sp. associated with soft coral *Sinularia polydactyla* against *Streptococcus equi* subsp. *zooepidemicus*. Int. J. Pharmacol. 3, 170-174 (2007).
5. Thiel, V., Leininger, S., Schmaljohann, R., Brümmer, F., & Imhoff, J.F.: Sponge-specific bacterial associations in the Mediterranean sponge *Chondrilla nucula* (Demospongiae, Tetractinomorpha). Microbial Ecol. 54, 101-111 (2007).
6. Lang, G., Wiese, J., Schmaljohann, R. & Imhoff, J.F.: New pentaenes from the sponge-derived marine fungus *Penicillium rugulosum*: structure determination and biosynthetic studies. Tetrahedron 63, 11844-11849 (2007).
7. Jiang, Y., Tang, S.K., Wiese, J., Xu, L.H., Imhoff J.F. & Jiang, C.L.: *Streptomyces hainanensis* sp. nov., a novel member of the genus *Streptomyces*. Int. J. Syst. Evol. Microbiol. 57, 2694-2698 (2007).
8. Jiang, Y., Wiese, J., Xu, L-H., Imhoff, J.F. & Jiang, C.-L.: Marine Actinobacteria, an important source of novel secondary metabolites with bioactivities. Chinese Journal ofAntibiot. 32, 705-712 (2007).
9. Muscholl-Silberhorn, A., Thiel V. & Imhoff J.F.: Abundance and bioactivity of cultured sponge-associated bacteria from the Mediterranean Sea. Microbial Ecol. 55, 94-106 (2008).
10. Bartsch, I., Wiencke, C, Bischof, K., Buchholz, C. M., Buck, B. H., Eggert, A., Feuerpfeil, P., Hanelt, D., Jacobsen, S., Karez, R., Karsten, U., Molis, M., Roleda, M. Y., Schuber, H., Schumann, R., Valentin, K., Weinberger, F. & Wiese, J.: The genus *Laminaria* sensu lato: recent insights and developments. European J. Phycology 43:1-86 (2008).
11. Gärtner, A., Wiese J. & Imhoff J.F.: *Amphritea atlantica* gen. nov., sp. nov., a gammaproteobacterium from the Logatchev hydrothermal vent field. Int. J. Syst. Evol. Microbiol. 58, 34-39 (2008).
12. Jiang, Y., Wiese, J., Tang, S.K., Xu, L.H., Imhoff J.F. & Jiang, C.L.: *Actinomycetospora chiangmaiensis* gen. nov., sp. nov., a new member of the family Pseudonocardiaceae. Int. J. Syst. Evol. Microbiol. 58, 408-413 (2008).

13. Heindl, H., Wiese, J. & Imhoff, J.F.: *Tenacibaculum adriaticum* sp. nov., from bryozoans in the Adriatic Sea. Int. J. Syst. Evol. Microbiol. 58, 542-547 (2008).
14. Staufenberger, T., Wiese, J., Thiel, V. & Imhoff, J.F.: Phylogenetic analysis of bacteria associated with *Laminaria saccharina*. FEMS Microbiol. Ecol. 64, 65-77 (2008).
15. Mitova, M.I., Lang, G., Wiese, J. & Imhoff, J.F.: Subinhibitory concentrations of antibiotics induce phenazine production in a marine *Streptomyces* sp. J. Nat. Prod. 71, 824-827 (2008).
16. Wiese, J., Jiang, Y., Tang, S.K., Thiel, V., Schmaljohann, R., Xu, L.H., Jiang, C.-L. & Imhoff J.F: A new member of the family *Micromonosporaceae*, *Planosporangium flavigriseum* gen. nov., sp. nov. Int. J. Syst. Evol. Microbiol. 58, 1324-1331 (2008).
17. Yu, Z., Lang, G., Kajahn, I., Schmaljohann, R. & Imhoff J.F.: Scopularides A and B, cyclodepsipeptides from a marine sponge-derived fungus *Scopulariopsis brevicaulis*. J. Nat. Prod. 71, 1052-1054 (2008).
18. Lang, G., Kalvelage, T., Peters, A., Wiese, J. & Imhoff, J.F.: Linear and cyclic peptides from the entomopathogenic bacterium *Xenorhabdus nematophilus*. J. Nat. Products 71, 1074-1077 (2008).
19. Wiese, J., Thiel, V., Gärtner, A., Schmaljohann, R. & Imhoff, J.F.: *Kiloniella laminariae* gen. nov., sp. nov., a new alphaproteobacterium from the marine macroalga *Laminaria saccharina*. Int. J. Syst. Evol. Microbiol. 59, 350-356 (2009).
20. Hohmann, C., Schneider, K., Bruntner, C.G., Brown, R., Jones, A.L., Goodfellow, M., Krämer, M., Imhoff, J.F., Nicholson, G., Fiedler, H.-P. & Süssmuth, R.D.: Albidopyrone, a new alpha-pyrone containing metabolite from marine-derived *Streptomyces* sp. NTK 227. J. Antibiot. 62, 75-79 (2009).
21. Hohmann, C., Schneider, K., Bruntner, C., Irran, E., Nicholson, G., Bull, A.T., Jones, A.L., Brown, R., Stach, J.E.M., Goodfellow, M., Beil, W., Krämer, M., Imhoff, J.F., Süssmuth, R.D. & Fiedler, H.-P.: Caboxamycin, a new antibiotic of the benzoxazole family produced by the deep sea strain *Streptomyces* sp. NTK 937. J. Antibiot. 62, 99-104 (2009).
22. Wiese, J., Thiel, V., Nagel, K., Staufenberger, T. & Imhoff, J.F.: Diversity of antibiotic-active bacteria associated with the brown alga *Laminaria saccharina* from the Baltic Sea. Mar. Biotechnol. 11, 287-301 (2009).
23. Lachnit, T., Blümel, M., Imhoff, J.F. & Wahl, M.: Specific epibacterial communities on macroalgae: phylogeny matters more than habitat. Aquatic Biology 5, 181-186 (2009).
24. Jiang, Y., Wiese, J., Cao, Y.-R., Xu, L.-H., Imhoff, J.F. & Jiang, C.-L.: *Promicromonospora flava* sp. nov., isolated from sediment of the Baltic Sea. Int. J. Syst. Evol. Microbiol. 59, 1599-1602 (2009).
25. Helaly, S., Schneider, J., Nachtigall, J., Vikineswary, S., Tan, G.Y.A., Zinecker, H., Imhoff, J.F., Süssmuth, R.D. & Fiedler, H.P.: Gombapyrones, new α-pyrone metabolites produced by *Streptomyces griseoruber* Acta 3662. J. Antibiot. 62, 445-452 (2009).
26. Schulz, D., Nachtigall, J., Riedlinger, J., Schneider, K., Poralla, K., Imhoff, J.F., Beil, W., Nicholson, G., Fiedler H.-P. & Süssmuth, R.: Piceamycin and its *N*-acetylcysteine adduct are produced by *Streptomyces* sp. GB 4-2. J. Antibiot. 62, 513-518 (2009).

27. Heindl, H., Wiese, J. & Imhoff, J.F.: Phylogenetic diversity and antimicrobial activities of bryozoan-associated bacteria isolated from Mediterranean and Baltic Sea habitats. Syst. Appl. Microbiol. 33, 94-104 (2010).
28. Paululat, T., Kilik, A., Hausmann, H., Karagouni, A.D., Zinecker, H., Imhoff, J.F. & Fiedler, H.-P.: Grecocyclines, new Angucyclines from *Streptomyce*s sp. Acta 1362. Eur. J. Org. Chem. 12, 2344-2350 (2010).
29. Schneemann, I., Nagel, K., Kajahn, I., Labes, A., Wiese, J. & Imhoff, J.F.: Comprehenisve investigation of marine actinobacteria associated with the sponge *Halichondria panicea*. Appl. Environ. Microbiol. 76, 3702-3714 (2010).
30. Goecke, F., Labes, A., Wiese, J. & Imhoff, J.F.: Chemical interactions between marine macroalgae and bacteria. Review Mar. Ecol. Prog. Ser. 409, 267-300 (2010).
31. Schneemann, I., Kajahn, I., Ohlendorf, B., Zinecker, H., Erhard, A., Nagel, K., Wiese, J. & Imhoff, J.F.: Mayamycin, a cytotoxic polyketide from a *Streptomyces* strain isolated from the marine sponge *Halichondria panicea*. J. Nat. Products 73, 1309-1312 (2010).
32. Nachtigall, J., Schneider, K., Nicholson, G., Goodfellow, M., Zinecker, H., Imhoff, J.F., Süssmuth, R.D. & Fiedler, H.-P.: Two new aurachins from *Rhodococcus* sp. Acta 2259. J. Antibiot. 63, 567-569 (2010).
33. Schneemann, I., Ohlendorf, B., Zinecker, H., Nagel, K., Wiese J. & Imhoff, J.F.: Nocapyrones A - D, γ-Pyrones from a marine *Nocardiopsis* strain isolated from the marine sponge *Halichondria panicea*. J. Nat. Prod. 73, 1444-1447 (2010).
34. Nachtigall, J., Schulz, D., Beil, W., Süssmuth, R.D. & Fiedler, H.P. 2010: Aranciamycin anhydride, a new anthracycline-type antibiotic isolated from *Streptomyces* sp. Tü 6384. J. Antibiot. 63, 397-399.
35. Neulinger, S.C., Stöhr, R., Thiel, V., Schmaljohann, R. & Imhoff, J.F.: New phylogenetic lineages of the *Spirochaetes phylum* associated with *Clathrina* species (Porifera). J. Microbiol. 48, 411-418 (2010).
36. Shaker, K., Morsy, N., Zinecker, H., Imhoff, J.F. & Schneider, B.: Secondary metabolites from *Calotropis procera* (Aiton). Phytochem. Lett. 3, 212-216 (2010).
37. Bringmann, G., Lang, G., Bruhn, T., Schäffler, K., Steffens, S., Schmaljohann, R., Wiese, J. & Imhoff, J.F.: Sorbifuranones A-C, sorbicillinoid metabolites from *Penicillium* strains isolated from Mediterranean sponges. Tetrahedron 53, 9894-9901 (2010).
38. Shaker, K.H., Zinecker, H., Ghani, M.A., Imhoff, J.F., & Schneider, B.: Bioactive metabolites from the sponge *Suberea* sp. Chem. Biodiv. 7, 2880-2887 (2010).
39. Gärtner, A., Ohlendorf, B., Schulz, D., Zinecker, H., Wiese, J. & Imhoff, J. F.: Levantilides A and B, 20-membered macrolides from a *Micromonospora* strain isolated from the Mediterranean deep-sea sediment. Mar. Drugs 9, 98-108 (2011).
40. Schulz, D., Ohlendorf, B., Zinecker, H., Schmaljohann, R. & Imhoff, J.F.: Eutypoids B−E produced by a *Penicillium* sp. strain from the North Sea. J. Nat. Prod. 74, 99-101 (2011).
41. Brötz, E., Kulik, A., Vikineswary, S., Lim, C.T, Tan, G.Y.A., Zinecker, H., Imhoff, J.F., Paululat, T. & Fiedler, H.-P.: Phenelfamycins G and H, new elfamycin-type antibiotics produced by *Streptomyces albospinus* Acta 3619. J. Antibiot. 64, 257-266 (2011).

42. Wiese, J., Ohlendorf, B., Blümel, M., Schmaljohann, R. & Imhoff, J.F.: Phylogenetic identification of fungi isolated from the marine sponge *Tethya aurantium* and identification of their secondary metabolites. Mar. Drugs 9, 561-585 (2011).

43. Fan, L., Bo S., Chen, H., Ye, W., Kleinschmidt, K., Baumann, H.I., Imhoff, J.F., Kleine, M. & Cai, D.: Genome sequence of *Bacillus subtilis subsp. spizizenii* gtP20b isolated from the Indian Ocean. J. Bac. 193, 1276-1277 (2011).

44. Imhoff, J.F., Labes, A. & Wiese, J.: Biomining the microbial treasures of the ocean: new natural products. Biotechnol Advances 29, 468-482 (2011).

45. Schneemann, I., Wiese, J., Kunz, A. & Imhoff, J.F.: Genetic approach for the fast discovery of phenazine producing marine Actinobacteria. Mar. Drugs 9, 772-789 (2011).

46. Nachtigall, J., Schneider, K., Bruntner, C., Bull, A.T., Goodfellow, M., Zinecker, H., Imhoff, J. F., Nicholson, G., Irran, E., Süssmuth, R. D. & Fiedler H.-P.: Benzoxacystol, a benzoxazine-type enzyme inhibitor from the deep-sea strain *Streptomyces* sp. NTK 935. J. Antibiot. 64, 453-457 (2011).

47. Kim, B.-Y., Willbold, S., Kulik, A., Helaly, S.E., Zinecker, H., Wiese, J., Imhoff, J.F., Goodfellow, M., Süssmuth, R. & Fiedler, H.-P.: Elaiomycins B and C, novel alkylhydrazides produced by *Streptomyces* sp. BK 190. J. Antibiot. 64, 595-597 (2011).

48. Jiang, Y., Cao, Y.-R., Wiese, J., Tang, S.-K., Xu, L.H**.,** Imhoff, J.F**.** & Jiang, C.L.**:** *Streptomyces sparsus* sp. nov., isolated from a alkaline and saline soil. Int. J. Syst. Evol. Microbiol. 61, 1601-1605 (2011).

49. Fan, L., Liu,Y., Li, Z., Baumann, H.I., Kleinschmidt, K., Ye, W., Imhoff, J.F., Kleine, M. & Cai, D.: Draft genome sequence of the marine *Streptomyces* sp. strain PP-C42 isolated from the Baltic Sea. J. Bacteriol. 193, 3691-3692 (2011).

50. Ohlendorf, B., Simon, S., Wiese, J. & Imhoff, J.F.: Szentiamide, an N-formylated cyclic depsipeptide from *Xenorhabdus szentirmaii* DSM 16338^{T}. Nat. Prod Comm. 6, 1247-1250 (2011).

51. Gärtner, A., Blümel, M., Wiese, J. & Imhoff, J.F.: Isolation and characterization of bacteria from the Eastern Mediterranean deep sea. Ant. Leeuwenhoek 100, 421-435 (2011).

52. Schulz, D., Beese, P., Ohlendorf, B., Erhardt, A., Zinecker, H., Dorador, C. & Imhoff, J.F.: Abenquins, aminoquinone derivatives produced by *Streptomyces* sp. strain DB634. J. Antibiot. 64, 763-768 (2011).

53. Nachtigall, J., Kulik, A., Bull, A.T., Goodfellow, M., Asenjo, J.A., Maier, A., Wiese, J., Imhoff, J.F., Süssmuth, R.D. & Fiedler, H.-P.: Atacamycins A-C, 22-membered antitumor macrolactones from *Streptomyces* sp. C38. J. Antibiot. 64, 775-780 (2011).

54. Staufenberger, T., Labes, A. & Imhoff, J.F.: First crenarchaeal chitinase found in *Sulfolobus tokodaii*. Microbiol. Res. 167, 262-269 (2012).

55. Heindl, H., Thiel, V., Wiese, J. & Imhoff, J.F.: Bacterial isolates from the bryozoan *Membranipora membranacea:* influence of culture media on microbial activity. Intern. Microbiol. 15, 17-32 (2012).

56. Goecke, F., Labes, A., Wiese, J. & Imhoff, J.F.: Dual effects of macroalgal extracts on growth of bacteria in the Western Baltic Sea. Rev. Biol. Mar. Oceanograf. 47, 75-86 (2012).

57. Helaly, S.E., Kulik, A., Zinecker, H., Ramachandaran, K., Tan, A., Imhoff, J.F., Süssmuth, R.D., Fiedler, H.-P. & Vikineswary, S.: Langkolide, a 32-membered macrolactone antibiotic produced by *Streptomyces* sp. Acta 3062. J. Nat. Prod. 75, 1018- 1024 (2012).
58. Schulz, D., Nachtigall, J., Geisen, U., Kalthoff, H., Imhoff, J.F., Fiedler H.-P. & Süssmuth, R.: Silvalactam, a 24-membered macrolactam antibiotic produced by *Streptomyces* sp. Tü 6392. J. Antibiot. 369-372 (2012).
59. Ohlendorf, B., Schulz, D., Erhard, A., Nagel, N. & Imhoff, J.F.: Geranylphenazinediol: an acetylcholinesterase inhibitor produced by a *Streptomyces* species. J. Nat. Prod. 75, 1400-1404 (2012).
60. Wahl, M., Goecke, F.R., Labes, A., Dobetsov, S. & Weinberger, F. 2012: The second skin: ecological role of epibiotic biofilms on marine organisms. Frontiers in Microbiol. 3, article no. 292.
61. Ohlendorf, B., Schulz, D., Beese, P., Erhard, A., Schmaljohann, R. & Imhoff, J.F.: Diacidene, a polyene dicarboxylic acid from a *Micromonospora* isolate from the German Wadden Sea. Z. Naturforsch. 67c, in press (2012).
62. Nagel, K., Schneemann, I., Kajahn, I., Labes, A., Wiese, J. & Imhoff, J.F. Proposed beneficial effects of 2,4-diacetylphloroglucinol-producing pseudomonads on the marine alga *Saccharina latissima*. Aquat. Microbiol. Ecol., in press (2012)
63. Goecke, F., Labes, A., Wiese, J., Schmaljohann, R. & Imhoff, J.F.: Observation of bacteria over the surface of released oogonia from *Fucus vesiculosus* L (Phaeophyceae). Gayana Botanica, in press (2012).
64. Goecke, F., Thiel, V., Wiese J. & Imhoff, J.F.: Algae as an important environment for bacteria - phylogenetic relationships among bacterial species isolated from algae. Phycologia, in press (2012).
65. Goecke, F., Labes, A., Wiese, J. & Imhoff, J.F.: Phylogenetic analysis and antibiotic activity of bacteria isolated from the surface of two co-occurring macroalgae from the Baltic Sea. Eur. J. Phycol. (in press).
66. Goecke, F., Wiese, J., Nunez, A., Labes, A., Imhoff, J.F. & Neuhäuser, S.: A novel phytomyxean parasite associated with galls on the bull-kelp *Durvillaea antarctica* (Chamisso) Hariot, PLOS ONE (in press).
67. Manderscheid, N., Soleiman, E.H., Kulik, A., Wiese, J., Imhoff, J.F., Fiedler, H.-P. & Süssmuth, R.D.: Elaiomycins D and E, new azoxy antibiotics from *Streptomyces* sp. Tü 6399. J. Antibiotics (in press).

Other scientific publications

Imhoff, J.F. & Wiese, J.: Blaue Biotechnologie auf dem Vormarsch. Neue Wirkstoffe aus Meeresorganismen. BIOforum 30, 36-37 (2008).

Imhoff, J.F. & Wiese, J.: Meeresorganismen als Quelle neuer Krebsmittel. Die Naturheilkunde. Forum Komplementäre Onkologie 86, 6-8 (2009).

Zinecker, H. & Imhoff, J.F. (2010) Bioassays für die Wirkstoffsuche aus dem Meer: Biologische Testsysteme zur Charakterisierung neuer Wirkstoffe. GIT Labor-Fachzeitschrift, 54. Jahrgang, Oktober 2010

Patents

Bringmann, G. Lang, G., Gulder, T., Schaumann, K., Steffens, S., Imhoff, J.F., Müller, W.E.G. & Perovic, S.: Sorbifuranone, Sorbivineton, Sorbivinetol und Derivate dieser Verbindungen, Verfahren zu ihrer Herstellung, sie enthaltende Arzneimittel und deren Verwendung. DE102004005106A1 (2005)

Bringmann, G., Lang, G., Gulder, T., Müller, W.E.G., Perovic, S., Schaumann, K., Imhoff, J.F., Stöhr, R., Wiese, J. & Schmaljohann, R.: Verfahren zur Produktion und Aufreinigung von Sorbicillacton A. DE102004004901A1 (2005)

Bringmann, G., Lang, G., Gulder, T., Müller, W.E.G., Perovic, S., Schaumann, K., Imhoff, J.F., Stöhr, R., Wiese, J. & Schmaljohann, R.: Method for producing sorbicillactone A. EP1713455A2 (2006)

Bringmann, G., Lang, G., Gulder, T., Müller, W.E.G., Perovic, S., Schaumann, K., Imhoff, J.F., Stöhr, R., Wiese, J. & Schmaljohann, R.: Method for producing sorbicillactone A. US2007135515A1 (2007)

Bringmann, G., Lang, G., Gulder, T., Müller, W.E.G., Perovic, S., Schaumann, K., Imhoff, J.F., Stöhr, R., Wiese, J. & Schmaljohann, R.: Method for producing sorbicillactone A. US2007135515A1 (2007)

Imhoff, J.F., Yu, Z., Lang, G., Wiese, J., Kalthoff, H. & Klose, S.: Herstellung und Verwendung antitumoraler Cyclodepsipeptide. DE10200800097 (2009)

Imhoff, J.F., Yu, Z., Lang, G., Wiese, J., Kalthoff, H. & Klose, S.: Production and use of antitumoral cyclodepsipeptides. EP2229401 (2010)

Imhoff, J.F., Kajahn, I., Lang, G., Wiese, J. & Peters, A.: Herstellung und Verwendung antitumoraler, antibiotischer und insektizider Cyclodepsipeptide. DE102009025119 (2010)

Imhoff, J.F., Kajahn, I., Lang, G., Wiese, J. & Peters, A.: Production and use of antitumoral, antibiotic and insecticidal cyclodepsipeptides WO/2010/142258 (2010)

Imhoff, J.F., Wiese, J., Zinecker, H., Kajahn, I., Nagel, K. & Schneemann, I.: Herstellung und Verwendung antibakterieller, antiproliferativer und antiphytopathogener Benzanthrine. DE102010006245 (2011)

Imhoff, J.F., Wiese, J., Zinecker, H., Kajahn, I., Nagel, K. & Schneemann, I.: Production and use of antibacterial, antiproliferative, and antiphytopathogenic benzanthracenes. WO/2011/091778 (2011)

Presentations on Scientific Symposia

Oral presentations on scientific symposia

Baumann, H.I., Wiese, J. Gärtner, A., Goecke, F., Heindl, H., Kajahn, I., Kleinschmidt, K., Labes, A, Nagel, K., Neulinger, S., Ohlendorf, B., Schneemann, I., Schulz, D., Staufenberger, T., Thiel, V., Zinecker, H. & Imhoff, J.F.: Biological role of secondary metabolites from marine microorganisms. VAAM-Symposium "Symbiotische Interaktionen", München, 20.11.2009

Baumann, H.I.: Isolierung, Charakterisierung und Produktion antimikrobieller Peptide (AMPs) mariner Mikroorganismen. Jahrestagung Biokatalyse2021, Kiel, 18.-19.10.2010

Goecke, F., Labes, A., Wiese, J. and Imhoff, J.F.: Bacteria Associations with Co-Occurring Macroalgae: Host, Epiphyte and Environmental Factors. 5th European Phycological Congress, Rhodes, Greece, 04-09 Sept. 2011

Goecke, F., Staufenberger, T., Wiese, J., Labes, A. & Imhoff, J.F.: "Differences in bacterial association with macroalgae are product of environmental and chemical interactions." (Diferencias de asociación bacteriana en macroalgas son producto de interacciones químicas y ambientales.) Third Latin-American Congress of Algal Biotechnology, Concepción, Chile, 16.-18.1. 2012

Goecke, F., Wiese, J., Labes, A. and Imhoff, J. F.: Interactions between macroalgae and bacteria: Bacterial communities associated to two baltic macroalgae. 5th International Student Conference: Biodiversity and functioning of aquatic ecosystems in the Baltic Sea region, Klaipeda, Lithuania, 6.-8.10.2010

Heindl, H., Wiese, J. and Imhoff, J.F.: Marine bryozoan-associated microorganisms: antibiotic properties and phylogenetic classification. 15th International Bryozoology Association Conference, Kiel, 2.-6.8.2010

Imhoff, J.F., Labes, A., Kajahn, I., Krämer, M., Stöhr, R., Thiel, V. and Wiese, J. "Marine biotechnology: bio-mining the treasures of the ocean." European Bioperspectives, Hannover, 7.10.2008

Imhoff, J.F.: "Biomining the treasure of the ocean – new natural products." VAAM Intern. Workshop "Biology and Chemistry of Antibiotic-Producing Bacteria". TU Berlin, 28.9.2008

Imhoff, J.F.: „Kieler Wirkstoff-Zentrum KiWiZ", Tübinger Gespräche zur Biologie und Chemie von Mikroorganismen, Heinrich-Fabri-Institut der Universität Tübingen, Blaubeuren, 24.7.2009

Imhoff, J.F.: „Wirkstoffe aus marinen Pilzen". Workshop „Tübinger Gespräche zur Biologie und Chemie von Mikroorganismen. Heinrich-Fabri-Institut der Universität Tübingen, Blaubeuren, 20.-22.7.2011

Imhoff, J.F.: Biomining: The treasure of the ocean. International Symposium on Ocean Science, Technology and Policy, Manado, Indonesien, 12.-14.5.2009

Imhoff, J.F.: Blue Biotechnology in Germany - the Kiel Centre for Marine Natural Products. Blue Biotech Cooperation Event, Kiel, Germany, 9.-10.5.2012

Imhoff, J.F.: Das Kieler Wirkstoffzentrum (KiWiZ) – Konzeption und Forschung. 1st Internat. Symposium on Sponge Microbiology, Universität Würzburg, 21.-22.3.2011

Imhoff, J.F.: Leuchtturmprojekt des Landes Schleswig-Holstein. Kieler Zentrum für Marine Wirkstoffe: Meeresorganismen als Wirkstoffproduzenten. Neues aus dem Meer – Marine Wirkstoffe, Büsum, Germany, 12.10.2006

Imhoff, J.F.: Life at hydrothermal vents – What do we know about it? Symposium: Biodiversity and Genetic Resources of the Deep Sea, Internationaler Seegerichtshof Hamburg, 29.9.2007

Imhoff, J.F.: Meeresorganismen als Fundgrube neuer Wirkstoffe. IHK Nord – Biotechnologiekonferenz, Schloss Fleesensee / Neubrandenburg, 10.4.2008

Imhoff, J.F.: Natural Products from bacteria associated with marine sponges and algae. ESF-COST High Level Research Conference, Hotel Villa del Mare, Acquafredda di Maratea, Italien, 20.-25.6.2010

Imhoff, J.F.: Strategie und Profil des Kieler Wirkstoff-Zentrums. DECHEMA-Tagung der Fachgruppe Algen, Frankfurt, 28.6.2012

Jansen, N.: Chlorazaphilone isoliert aus *Bartalinia robillardoides*. Workshop „Tübinger Gespräche zur Biologie und Chemie von Mikroorganismen. Heinrich-Fabri-Institut der Universität Tübingen, Blaubeuren, 20.-22.7.2011

Jansen N.: Aufarbeitung von Naturstoffextrakten mittels chromatographischer Methoden. Chrom Forum Hamburg von VWR International, Hamburg, Germany, 29.2.2012

Jansen N.: Aufarbeitung von Naturstoffextrakten mittels chromatographischer Methoden. Chrom Forum Hamburg von VWR International, Steinfurt, Germany, 28.9.2012

Jansen N.: Aufarbeitung von Naturstoffextrakten mittels chromatographischer Methoden. Chrom Forum Hamburg von VWR International, Darmstadt, Germany, 6.11.2012

Kleinschmidt, K.: Screening nach antimikrobiellen Peptiden. Tübinger Gespräche zur Biologie und Chemie von Mikroorganismen, Heinrich-Fabri-Institut der Universität Tübingen, Blaubeuren, 24.7.2009

Labes A.: Bio-mining the microbial treasures of the ocean. Early drug discovery and models for entering pharmaceutical pipelines. Rende-vouz de Concarneau, Concarneau, France, 29.-30.8.2012

Labes A.: Bio-mining the microbial treasures of the ocean. Early drug discovery and models for entering pharmaceutical pipelines. MarineBiotech, Workshop Mobilisation and Engagement of Funding Agencies and Stakeholders, Faro-Olhão, Portugal, 26.-27.4.2012

Labes A.: Genome based methods for the exploration of natural products from marine fungi for the treatment of cancer. Blue Biotech Cooperation Event, Kiel, Germany, 9.-10.5.2012

Labes A.: Wenn sich Bakterien unterhalten – Bakterielle Interaktionen (im Meer). 2. LifeSciene Conference Analytik Jena, Jena, Germany, 3.-4.5.2012

Labes, A., Imhoff, J.F.: Genome based methods for the exploration of natural products from marine fungi for the treatment of cancer, ProkaGenomics, Göttingen, 18.-22.9.2011

Labes, A., Oesterwalbesloh, J. & Imhoff J.F.: Secondary metabolites from deep sea bacteria: an efficient route for biodiscovery from extreme habitats. Extremophiles, Sevilla, Spain, 10.-13.9.2012

Labes, A., Staufenberger, T. and Imhoff, J.F., 2008: „Novel glycoside hydrolases for biotechnological application from marine resources". BioCat2008-Tagung, Hamburg, 03.08.2008

Labes, A: . Schätze aus dem Ozean: Neue Naturstoffe aus marinen Mikroorganismen. 1. Life Science Conference der Analytic Jena, 5.-.6.5.2010

Neulinger, S.C.: The microbiology of *Lophelia pertusa*. OLF 2010 cold-water coral workshop, 2010, Stavanger, Norway. 31.5.-1.6.2010

Schulz, D.: Exploring Microorganisms from Marine Environments – Building a natural products library. VAAM Workshop, Bonn, 28.09.2011

Silber, J.: Naturstoffe von Pilzen aus dem Wattenmeer. Workshop „Tübinger Gespräche zur Biologie und Chemie von Mikroorganismen. Heinrich-Fabri-Institut der Universität Tübingen, Blaubeuren, 20.-22.7.2011

Staufenberger, T., Labes, A. and Imhoff, J.F.: Novel thermoacidophilic chitinase from the crenarchaeon *Sulfolobus tokodaii*. 9th International Conference of the European Chitin Society, Venedig, Italien, 26.5.2009

Stöhr, R., and Imhoff, J.F.: Production of Sorbicillacton A. Marie-Curie Summer school, Rovinj, Kroatien, 24.08.2006

Wiese, J.: Blue Biotechnology all around the Baltic Sea. Blue Biotech Cooperation Event, Kiel, Germany, 9.-10.5.2012

Zinecker, H.: Bioassays am Kieler Wirkstoff-Zentrum. Tübinger Gespräche zur Biologie und Chemie von Mikroorganismen, Heinrich-Fabri-Institut der Universität Tübingen, Blaubeuren, 24.7.2009

Poster presentations on scientific meetings

Antosch, A., Engeser, M., Wiese, J., Imhoff, J.F., Fiedler, H.-P. and T.A.M. Gulder. Isolation and characterization of cyclohepatamycins A-C. VAAM-Workshop, Biology and Chemistry of Antibiotic-Producing Bacteria and Fungi, Braunschweig, Germany, 27.-29.09.2012

Brötz, E., Herrmann, J., Maier, A., Kelter, G., Wiese, J., Zinecker, H., Imhoff, J.F., Müller, R. & Paululat, T.: Structure-activity-relationship of Grecoketidone and related naphthoquinones. VAAM-Meeting “Biology of Bacteria Producing Natural Compounds”, 28.-30.9.2011

Gärtner, A., Krämer, M., Kajahn, I., Labes, A., Nagel, K., Stöhr, R., Schmaljohann, R., Schneemann, I., Thiel, V., Wiese, J. & Imhoff, J.F.: Exploiting the pharmaceutical potential of Marine Microorganisms. XXX. Congreso Chileno de Microbiología, Concepción, Chile, 4.-6.12.2008.

Gärtner, A., Wiese, J. & Imhoff, J.F.: *Amphrite atlantica*, a novel representative of the Oceanospirillaceae. VAAM-Jahrestagung, Osnabrück, 01.04.-04.04.2007

Goecke F., Thiel, V., Wiese, J., Labes, A. & Imhoff, J.F.: Phylogenetic relationships among bacteria described from algae: Algae are a distinct source of new taxa. Third Latin-American Congress of Algal Biotechnology, Concepción, Chile, 16.-18.1. 2012

Goecke, F., Labes, A., Wiese, J. & Imhoff, J.F. Insights supporting the proposal of possible ‘symbiotic role’ of marine bacteria on macroalgae. Symposium Microbial Interactions in Marine Systems (MIMAS), Greifswald, 6.7.-8.7.2011

Goecke, F., Labes, A., Wiese, J. & Imhoff, J.F.: Bacteria associated with coexisting macroalgae: seasonal, interspecies variation and antibiotic effects. VAAM-Jahrestagung, Karlsruhe, 3.-6.4.2011

Goecke, F., Perez, A., Cabrera, A. & Baez, P.: Factores que modulan la biodiversidad de la epifauna asociada a macroalgas comunes de Chile central. XXX Congreso de Ciencias del Mar, Concepcion, Chile, 19.-22.10.2010

Goecke, F., Staufenberger, T., Wiese, J., Gärtner, A., Thiel, V., Nagel, K., Blümel, M., Schmaljohann, R. & Imhoff, J.F.: Macroalgae as source of new species of microorganisms, 11th Young Systematists Forum, The Natural History Museum London, 2.12.2009

Goecke, F., Thiel, V., Wiese, J., Labes, A. & Imhoff, J.F.: Phylogenetic relationships among bacteria described from algae: Distinct source of new taxa. VAAM-Jahrestagung, Tübingen, Germany, 18.-21.3. 2012

Goecke, F., Wiese, J., Labes, A. & Imhoff, J.F.: Variability of the algae-associated bacterial communities among coexisting *Fucus vesiculosus* (Phaephyceae) and *Delesseria sanguinea* (Rhodophyta) in the Baltic Sea. VAAM-Jahrestagung ,Bochum, 8.-11.3.2009

Heindl, H., Schneemann, I., Wiese, J. & Imhoff, J.F.: *Tenacibaculum adriaticum*, a new Bryozoan-associated bacterium with specific antibiotic activities. VAAM-Jahrestagung, Frankfurt, 09.-11.03.2008

Heindl, H., Wiese, J., Nikulina, E. & Imhoff, J.F.: Bryozoan-associated bacteria with antibiotic activities. VAAM-Jahrestagung, Osnabrück, 01.-04.04.2007

Hong, H., Correa, J., Eguereva, E., Wiese, J., Imhoff, J.F., Gross, H. and T.A.M. Gulder. Total synthesis and stereochemical characterization of lajollamide A from the marine fungus *Asteromyces cruciatus*. VAAM-Workshop, Biology and Chemistry of Antibiotic-Producing Bacteria and Fungi, Braunschweig, Germany, 27.-29.09.2012

Imhoff, J.F. & Wiese, J.: FIT 2007 mit dem Schwerpunkt "Onkologie in Norddeutschland und Neue Therapieansätze in Forschung und Praxis", 1.11.2007 im Schulauer Fährhaus in Wedel (Schleswig-Holstein).

Imhoff, J.F.: Kieler Wirkstoff-Zentrum: Research on Marine Natural Products. Cluster retreat “The Future Ocean”, Salzau, 31.3.-1.4.2009

Imhoff, J.F.: Marine Natural Products: Sources, structure analyses, biological role and applications. “Inflammation at Interfaces”, 2nd International Conference of the Cluster of Excellence, Kiel, 9.-11.7.2009

Jansen, N. & Imhoff, J.F.: "Chlorazaphilone isolated from *Bartalinia robillardoides*“ Congress of European Microbiolgists, FEMS 2011, Genf, Schweiz, 26.-30.6.2011

Jansen, N., Schulz, D., Kajahn, I. & Imhoff, J.F.: Secondary metabolites produced by fungi isolated from a marine sponge. IMC9 The Biology of Fungi, Edinburgh, UK, 1.-6.8.2010

Jiang, Y., Wiese, J., Tang, S.K., Xu, L.H., Imhoff, J.F. & Jiang, C.L.: *Actinostreptospora chiangmaiensis* gen. nov., sp. nov., a new member of the family Pseudonocardiaceae. VAAM-Jahrestagung, Osnabrück, 01.-04.04.2007

Kajahn, I. & Imhoff, J.F.: Isolation and structure elucidation of novel bioactive peptides from marine fungi and bacteria. European Bioperspectives, Hannover, 7.-10.10.2008

Kajahn, I., Zhiguo, Y, Lang, G., Schmaljohann, R. & Imhoff, J.F. Scopularides A and B, two new cyclodepsipeptides from the marine sponge-derived fungus *Scopulariopsis brevicaulis*. 7th Joint Meeting of AFERP, ASP, GA, PSE & SIF, Natural Products with pharmaceutical, nutraceutical, cosmetic and agrochemical interest, Athen, 3.-8.8.2008

Kleinschmidt, K., Gärtner, A., Baumann, H.I. & Imhoff, J.F.: Marine *Bacillus amyloliquefaciens* strains: promising source for antimicrobial peptides. VAAM Jahrestagung, Hannover, 28.-31.3.2010

Kleinschmidt, K., Gärtner, A., Baumann, H.I. & Imhoff, J.F.: Searching for antimicrobial peptides in bacteria from the Baltic Sea. Summer School in Applied Molecular Microbiology, Dubrovnik, Kroatien 21.-29.08.2010

Kramer, A. Labes, A., Wiese, J., Ohlendorf, B. & Imhoff, J.F.: Secondary metabolites of fungi associated to the marine sponge *Halichondria panicea*, MIMAS Symposium, Greifswald, 6.-8.7.2011.

Kramer, A., Paun, L., Labes, A., Kempken, F. & Imhoff, J.F.: Development of a miniaturised screening method for fungal mutants with enhanced production of specific natural compounds. SUBMARINER Blue Biotechnology Cooperation Event: New Strategies and Future Perspectives. Kiel, Germany, 9.-10.5.2012

Krämer, M., Kajahn, I., Labes, A., Nagel, K., Stöhr, R., Schmaljohann, R., Schneemann, I., Thiel, V., Wiese J. & Imhoff J.F. Exploiting the pharmaceutical potential of Marine Microorganisms. International Congress on Biocatalysis, Hamburg, 31.8.-4.9.2008

Krämer, M., Labes, A., Lang, G., Schmaljohann, R., Stöhr, R., Wiese, J. & Imhoff, J.F.: Vom Extrakt zum Wirkstoffkandidaten. Neues aus dem Meer – Marine Wirkstoffe, Büsum, Germany, 12.10.2006

Krämer, M., Labes, A., Lang, G., Schmaljohann, R., Stöhr, R., Wiese, J. & Imhoff, J.F.: Leuchtturmprojekt des Landes Schleswig-Holstein. Kieler Zentrum für Marine Wirkstoffe: Meeresorganismen als Wirkstoffproduzenten. Neues aus dem Meer – Marine Wirkstoffe, Büsum, Germany, 12.10.2006

Krämer, M., Stöhr, R., Lang, G., Labes, A., Schmaljohann, R., Wiese, J., Imhoff, J.F. : New Natural Products from Marine Microorganisms. European Bioperspectives 2007. Köln, 30.5.-1.6.2007

Krämer, M., Stöhr, R., Lang, G., Labes, A., Schmaljohann, R., Wiese, J., Imhoff, J.F. : New Natural Products from Marine Microorganisms – Zentrum für Marine Wirkstoffe. Neues aus dem Meer – Lebensmittel/Nahrungsergänzungsmittel, WTSH, Büsum, 13.6.2007

Krämer, M., Thiel, V. & Imhoff, J.F. Selection of marine D-amino acid utilising microorganisms: a potential source for novel enzymes. International Congress on Biocatalysis, Hamburg, 31.8.-4.9.2008

Labes, A. & Imhoff, J.F.: Natural products from marine fungi for the treatment of cancer. VAAM-Jahrestagung, Karlsruhe, 3.-6.4.2011

Labes, A., Kajahn, I, Krämer, M., Stöhr., R., Thiel, V., Wiese, J. & Imhoff, J.F.: New natural products from marine microorganisms. Analytica, München, 1.-4.4.2008

Labes, A., Kajahn, I, Krämer, M., Stöhr., R., Thiel, V., Wiese, J. & Imhoff, J.F.: New natural products from marine microorganisms. European Bioperspectives, Hannover, 7.-10.10.2008

Labes, A., Klotz, H., Schneemann, I. & Imhoff, J.F.: Efficient screening for secondary metabolites in marine fungi using biosynthetic genes. CEBITEC Symposium, Bielefeld, 3.-5.5.2010

Labes, A., Klotz, H., Schneemann, I. & Imhoff, J.F.: Treasures of the ocean: Sustainable exploitation of the biotechnological potential of marine fungi. IMC9: The Biology of Fungi, Edinburgh, UK, 1.-6.08.2010

Labes, A., Kramer, A. & Imhoff, J.F: Genome based methods for the exploration of natural products from marine fungi for the treatment of cancer. 3rd AOI Symposium „Academic Drug Development in Oncology – Translating Basic Science Research into Innovative Treatments", Berlin, Germany, 16.11.2011

Labes, A., Staufenberger, T. & Imhoff, J.F., 2008: Novel glycoside hydrolases for biotechnological application from marine resources. VAAM-Jahrestagung, Frankfurt, 09.-11.03.2008

Lang, G, Kalvelage, T., Peters, A., Wiese, J. & Imhoff, J.F.: New linear and cyclic peptides from *Xenorhabdus nematophilus*. 56. Deutsche Pflanzenschutztagung: "Pflanzenproduktion im Wandel – Wandel im Pflanzenschutz?" Kiel, 22.-25.9.2008

Lang, G., Liedtke, J., Wiese, J., Stöhr, R. & Imhoff, J.F: Influence of culture conditions on the production of known and new bacillaenes by a marine sponge-derived *Bacillus subtilis*. V. European Conference on Marine Natural Products, Ischia. 16.-21.9.2007

Lang, G., Wiese, J., Schmaljohann, R. & Imhoff, J.F: Novel fungal pentaens from a sponge derived *Penicillium* sp. ManoproxXII. 12th International Symposium on Marine Natural Products, Queenstown, New Zealand, 4.-9.2.2007

Manderscheid, N., Helaly, S., Kulik, A., Kim, B-Y., Goodfellow, M., Wiese, J., Imhoff, J.F., Süssmuth, R.D. & Fiedler, H.-P. New elaiomycins produced by *Streptomyces* strains. VAAM-Jahrestagung, Tübingen, Germany, 18.-21.3. 2012

Mitova, M., Wiese, J. & Imhoff, J.F: Subinhibitory concentrations of antibiotcs induce phenazine production in a *Streptomyces* sp. isolate. V. European Conference on Marine Natural Products, Ischia. 16.-21.9.2007

Mitova, M.I., Lang, G., Wiese, J., Schneemann, I., Kajahn, I. & Imhoff, J.F.: Stimulation of the production of new phenazines in a marine *Streptomyces* sp. Isolate. VAAM-Jahrestagung, Frankfurt, 09.-11.03.2008

Muscholl-Silberhorn, A. & Imhoff, J.F.: Quantification of the cultured fraction of sponge-associated microorganism with respect to antimicrobial activity and ecological function. VAAM-Jahrestagung, Jena, 21.-22.3.2006

Nagel, K., Schneemann, I., Kajahn, I., Wiese, J., Labes, A. & Imhoff, J.F.: Pseudomonads in association with *Saccharina latissima* – evidence of a beneficial interaction in marine environments? International VAAM-Workshop „Biology of bacteria producing natural products", Tübingen, 26.-28.9.2010

Nagel, K., Schneemann, I., Kajahn, I., Wiese, J., Labes, A., Lang, G., Goecke, F., Thiel, V. & Imhoff, J.F.: Ecological impact of biologically active metabolites produced by *Laminaria saccharina* associated *Pseudomonas* sp. strains. VAAM-Jahrestagung, Bochum, 8.-11.3.2009

Nagel, K., Schneemann, I., Wiese, J., Kajahn, I., Labes, A. & Imhoff, J.F.: Ecological impact of biologically active metabolites produced by *Laminaria saccharina* associated *Pseudomonas* sp. strains. 6th European Conference on Marine Natural Products, Porto, Portugal, 19.-23.7.2009

Paululat, T., Kulik, A., Imhoff, J.F. & Fiedler, H.-P.: Grecocycline, a new angucycline from *Streptomyces* sp. Acta 1362, 21. Irseer Naturstofftage, Irsee 25.-27.2.2009

Schneemann, I., Gärtner, A., Wiese, J., Lang, G. & Imhoff, J.F. Novel marine bacteria as a source for promising natural products. VAAM-Workshop „Biology of Bacteria Producing Natural Products", Otzenhausen/Saarland, 4.-6.10.2007

Schneemann, I., Nagel, K., Mitova, M.I., Wiese, J. & Imhoff, J.F.: Molecular analysis and subsequent variation of culture conditions to discover new compounds from marine bacteria. Summer School "Microbial Secondary Metabolites: Genomes, Signals and Communities". Dubrovnik, Kroatien, 24.8.-1.9.2008

Schneemann, I., Wiese, J., Jiang, Y. & Imhoff, J.F.: PKS and NRPS genes in Actinomycetales from environmental samples. VAAM-Jahrestagung, Osnabrück, 01.-04.04.2007

Schulz, D., Mitova, M., Schneemann, I., Kajahn, I., Labes, A., Lang, G., Thiel, V., Wiese, J. & Imhoff, J.F.: Marine streptomycetes as source for new natural products. Biology of Streptomycetes, Universität Osnabrück, Tagungsort Münster, 7.-11.10.2009

Silber, J., Kajahn-Knopf, I., Jansen, N. & Imhoff, J.F.: Stimulation of secondary metabolite biosynthesis in a marine *Pestalotiopsis* sp. by modification of culture conditions. 9th International Mycological Congress (IMC9), Edinburgh, 05.08.2010

Silber, J., Knopf-Kajahn, I., Jansen, N. & Imhoff, J.F.: Secondary metabolites from a marine Pestalotiopsis isolate. IV. Congress of European Microbiologists FEMS, Genf, Schweiz, 26.-30.6.2011

Silber, J., Ohlendorf, B., Erhard, A., Labes, A., & Imhoff, J.F.: Secondary metabolites of fungi from the German Wadden Sea. VAAM-Jahrestagung, Tübingen, Germany, 18.-21.3. 2012

Staufenberger, T., Heindl, H., Gärtner, G., Labes, A. & Imhoff, J.F.: Screening for chitin degrading microorganism in different marine habitats. VAAM-Jahrestagung, Bochum, 8.-11.3.2009

Staufenberger, T., Klokman, V., Gärtner, A., Heind, H., Wiese, J., Labes, A. & Imhoff, J.F.: Extracellular bacterial chitinases from marine environments. VAAM-Jahrestagung, Karlsruhe, 3.-6.4.2011

Staufenberger, T., Wiese, J., Thiel, V. & Imhoff, J.F.: “Microbial communities of Laminaria saccharina observed in the North- and Baltic Sea.” ISME12 - 12th International Symposium on Microbial Ecology, Cairns (AU), 17.-22.08.2008

Staufenberger, T., Wiese, J., Thiel, V. & Imhoff, J.F.: Phylogenetic analysis of bacteria associated with *Laminaria saccharina*. VAAM-Jahrestagung, Osnabrück, 01.-04.04.2007

Stöhr, R., Krämer, M., Lang, G., Schmaljohann, R., Wiese, J. & Imhoff, J.F.: Pharmaceutical potencial of marine Microorganisms – Zentrum für Marine Wirkstoffe. Conference 2006 Marine Biotech, Greifswald, 21.-24.6.2006

Thiel, V. & Imhoff, J.F.: Sponge-associated bacterial diversity differs significantly between sponge species at the same location in the Adriatic Sea. International Symposia in Microbial Ecology, ISME-11, Wien, 20.-26.8.2006

Thiel, V., Muscholl-Silberhorn, A. & Imhoff, J.F.: “Antimicrobially active alphaproteobacteria associated with marine sponges – possible symbionts.” VAAM-Jahrestagung, Frankfurt, 09.-11.03.2008

Thiel, V., Staufenberger, T. & Imhoff, J.F.: Spatial distribution of sponge associated bacteria within *Tethya aurantia*. VAAM-Jahrestagung, Jena, 19.-22.3.2006

Wiese J., Thiel, V., Lang, G., Schneemann, I., Schubert, S. & Imhoff, J.F.: Actinomycetes derived from the marine sponge *halichondria panicea:* Phylogenetic diversity and antibiological activity. VAAM Biology of Bacteria Producing Natural Products, VAAM Workshop, Tübingen, 20.-22.10.2006

Wiese, J., Baumann, H.I., Kajahn, I., Labes, A., Ohlendorf, B., Schmaljohann, R., Schulz, D., Stöhr, R., Zinecker, H. & Imhoff, J.F.: Marine Biotechnology: Sustainable uses of marine bacteria and fungi. ESF-COST High Level Research Conference, Hotel Villa del Mare, Acquafredda di Maratea, Italien, 20.-25.6.2010

Wiese, J., Baumann, H.I., Labes, A., Ohlendorf, B., Schmaljohann, R., Schulz, D., Stöhr, R. & Imhoff, J.F.: New drugs in oncology from marine bacteria and fungi. AIO-Symposium „Academic Drug Development in Oncology – Translating Basic Science Research Into Innovative Treatments“, Berlin, 17.11.2010

Wiese, J., Gärtner, A, Heindl, H., Kajahn, I., Krämer, M., Labes, A., Lang, G., Mitova, M , Nagel, K., Schmaljohann, R., Schneemann, I., Stöhr, R., Thiel, V., Yu, Z. & Imhoff, J.F.: „Marine Microbial Resources – 2nd Bi-annual Symposium „The Future Ocean“, Kiel, 6.-9.10.2008.

Wiese, J., Gärtner, A, Heindl, H., Kajahn, I., Lang, G., Mitova, M., Nagel, K., Schmaljohann, R., Schneemann, I. & Imhoff, J. F.: “Marine habitats – promising sources of novel microorganisms and new natural products with biotechnological applications, 7th Joint Meeting of AFERP, ASP, GA, PSE & SIF, Natural Products with pharmaceutical, nutraceutical, cosmetic and agrochemical interest, Athen, 3.-8.8.2008

Wiese, J., Gärtner, A, Heindl, H., Kajahn, I., Lang, G., Mitova, M , Nagel, K., Schneemann, I., Thiel, V. & Imhoff, J.F.: “New antibiotic producing bacteria from marine environments. VAAM International Workshop “Biology and Chemistry of Antibiotic-Producing Bacteria”. Technische Universität Berlin, 29.9.-1.10.2008.

Wiese, J., Gärtner, A., Heindl, Lang, G., Nagel, K., Schmaljohann, R. & Imhoff, J.F.: Marine habitats are promising sources of novel microorganisms and newnatural products with biotechnological applications. Summer School “Microbial Secondary Metabolites: Genomes, Signals and Communities”, Dubrovnik, Croatia 24.8.-1.9.08.

Wiese, J., Labes, A. & Imhoff, J.F.: From Marine Ecology to Marine Biotechnology: Small bioactive molecules in biological interactions and biotechnological applications. Future Ocean Retreat, Schleswig, 22.-23.3.2010

Wiese, J., Radjasa, O., Ullmann, B., Guldner, T.A.M., Thiel, V., Schubert, S., Bringmann, G. & Imhoff, J.F.: Biological role of pseudomonic acid A produced by a sponge-symbiotic *Pseudomonas* strain. VAAM-Jahrestagung, Hannover, 28.3.-31.3.2010

Wiese, J., Schmaljohann, R., Thiel, V., Lang, G., Kalthoff, H., Klose, S., Müller, W.E.G., Schubert, S. & Imhoff, J.F.: Fungi from the marine sponge *Tethya aurantium*: identification and biological activity. VAAM-Jahrestagung, Osnabrück, 01.-04.04.2007

Wiese, J., Schulz, D., Stöhr, R., Nagel, K., Labes, A., Schneemann, I., Heindl, H., Jansen, N., Silber, J., Kramer, A., Goecke, F., Schmaljohann, R., Staufenberger, T., Gärtner, A., Baumann, H., Kleinschmidt, K. & Imhoff, J.F. Biologically active compounds from microorganisms derived from marine macroorganisms and marine sediments. NatPharma: Nature Aided Drug Discovery, NADD, Napoli, Italy, 5.-9.6.2011

Wiese, J., Thiel, V., Nagel, K., Staufenberger, T., Lang, G. & Imhoff, J.F: Production of antimicrobial compounds by alga derived marine bacterial isolates. Symposium on Chemistry and Biology of Bioactive Natural Products, Kaiserslautern, 19.-21.9.2007

Wiese, J., Thiel, V., Staufenberger, T., Lang, G. & Imhoff, J.F.: Epiphytic bacteria as producers of antimicrobial substances. European Conference on Marine Natural Products, Ischia, Italy, 16.-21.9.2007

Wiese, J., Thiel, V., Staufenberger, T., Stöhr, R. & Imhoff, J.F.: Microbial communities associated with the brown alga *Laminaria saccharina*. VAAM-Jahrestagung, Jena, 19.-22.3.2006

Zinecker, H., Wiese, J. & Imhoff, J.F.: Treasures of the ocean: natural products for medical applications. Ocean & Earth – past, present and future. Northcluster Workshop Series. Kiel, 08.-09.10.2009

Presentations to the Public

Oral presentations to stakeholders and the wider public

Baumann, H. I.: Workshop der Biokatalyse2021, TuTech Hamburg. Vorstellung der Ergebnisse des Projektes: „Isolierung, Charakterisierung und Produktion antimikrobieller Peptide (AMPs) aus marinen Mikroorganismen.“ Hamburg, 1.7.2011

Imhoff, J.F. Neue Naturstoffe aus dem Meer. Jungchemiker-Forum, Bonn, 11.7.2006

Imhoff, J.F.: “Neue Medikamente aus dem Meer”: Föhrde-Club zu Kiel, 16.10.2008

Imhoff, J.F.: „Marine Biotechnologie – Entwicklung neuer Produkte für Pharmazie, Kosmetik, Lebensmittel und Pflanzenschutz“. IHK und Zentrum für Marine Wirkstoffe KiWiZ, 9.4.2008

Imhoff, J.F.: „Marine biotechnology and research of active substances“, Seminar Auditorium Facultad de Recursos del Mar, Universidad de Antofagasta, 20.11.2008.

Imhoff, J.F.: Das Kieler Wirkstoffzentrum (KiWiZ) – Konzeption und Forschung. Institut für Organische Chemie, Tübingen. 22.2.2011

Imhoff, J.F.: Das Kieler Wirkstoff-Zentrum KiWiZ am IFM-GEOMAR. Aktuelles zur marinen Biotechnologie. Jahrestagung Biokatalyse2021, Kiel, 18.-19.10.2010.

Imhoff, J.F.: Das Meer als Schatztruhe für neue Wirkstoffe. Let Life Sciences meet you. Bundesweites Netzwerk von Studenten und Doktoranden der Life Sciences. Universität Lübeck, 21.5.2008

Imhoff, J.F.: Fachschaftstagung der Fachschaft Chemie-Biologie „Schatztruhe Ozean“: Marine Wirkstoffe, Historisch-Ökologische Cusanuswerk Bildungsstätte, Papenburg, 1.5.2008

Imhoff, J.F.: Leben unter Extrembedingungen. Schleswig-Holsteinische Universitätsgesellschaft Kiel. Albersdorf, 13.6.2006

Imhoff, J.F.: Marine Living Resources. Workshop InWaterTec Kiel 10.10.2007

Imhoff, J.F.: Medikamente aus dem Meer. Promega-Journalisten-Workshop Nationale Forschungsstrategie BioÖkonomie 2030 – Herausforderungen des 21. Jahrhunderts. TuTech Innovation GmbH, Hamburg, 19.5.2011

Imhoff, J.F.: Medikamente aus dem Meer. Schleswig-Holsteinische Universitätsgesellschaft Kiel. Kulturkreis Malente, 19.1.2006

Imhoff, J.F.: Medikamente aus dem Meer. Schleswig-Holsteinische Universitätsgesellschaft Kiel. Heimatmuseum Heiligenhafen, 15.3.2006

Imhoff, J.F.: Medikamente aus dem Meer. Schleswig-Holsteinische Universitätsgesellschaft Kiel. Naturkundemuseum Niebüll, 28.3.2006

Imhoff, J.F.: Medikamente aus dem Meer. Schleswig-Holsteinische Universitätsgesellschaft Kiel. Büsum, 28.9.2006

Imhoff, J.F.: Medikamente aus dem Meer. Schleswig-Holsteinische Universitätsgesellschaft Kiel. Universität Kiel, 13.11.2006

Imhoff, J.F.: Medikamente aus dem Meer. Schleswig-Holsteinische Universitätsgesellschaft Kiel. Kronshagen, 9.10.2007

Kajahn, I. and Imhoff, J.F. 2008: “Das Meer als Schatztruhe neuer Wirkstoffe’” 25. Chrom-Forum in Burgsteinfurt, 10.09.2008

Kajahn, I.: Das Meer als Schatztruhe neuer Wirkstoffe. Chrom Forum, Hochschule für Angewandte Wissenschaften, Hamburg, 18.2.2009

Kleinschmidt, K.: Antimikrobielle Peptide aus marinen Mikroorganismen. Workshop: Tübinger Gespräche zur Biologie und Chemie von Mikroorganismen, Heinrich-Fabri-Institut, Blaubeuren, 14.-16.7.2010

Kleinschmidt, K.: Jahresversammlung des Fördervereins des IFM-GEOMAR. “Antimikrobielle Peptide aus marinen Mikroorganismen” Part 1, Kiel, 14.2.2011

Kramer, A.: "Identification, bioactivity and biosynthesis of natural products from marine sponge associated fungi" Biocatalysis 2021, Summer School, Methods in Biotechnology: Milestones in products and process development, Kiel, 11.-14.07.2011

Krämer, M., Wiese, J., and Imhoff, J.F.: Blaue Biotechnologie am IFM-GEOMAR. Neue Medikamente aus dem Meer. Parlamentarischer Abend. Wasser, Leibniz-Gemeinschaft, Berlin, 30.5.2006

Kunz, A.: "Phenanzines produced by marine bacteria" Biocatalysis 2021, Summer School, Methods in Biotechnology: Milestones in products and process development, Kiel, 11.-14.07.2011

Labes A.: Neo-Nature – die neue Naturkosmetik. Beauty Düsseldorf, 20.3.2011

Labes, A., 2007: Neues aus dem Meer: Was können marine mikrobielle Ressourcen zur Nahrungsmittelveredlung beitragen? Neues aus dem Meer (WTSH), Büsum, Germany, 13.6.2007

Labes, A.: High added value products from marine microbes - northern Blue Biotech network. "Øresund Brokerage Rostock 2010", Rostock, 16.9.2010.

Labes, A.: Neue chemische Wertstoffe mit Enzymen aus marinen Organismen. IBN-Forum Hamburg, 22.2.2011

Labes A.: Meer Kosmetik. Neue Rohstoffe und Kosmetikkonzepte aus dem Meer – was können marine mikrobielle Ressourcen dazu beitragen? L'Oreal Pressekonferenz, Hamburg, Germany, 14.3.2012

Staufenberger, T., Labes, A. and Imhoff, J.F.: Chitin modifying enzymes. Gastredner im Seminar aquatische Mikrobiologie am Leibniz-Institut für Gewässerökologie und Binnenfischerei, Neuglobsow, 22.9.2009

Wiese, J., and Labes, A.: Schätze aus dem Ozean: Neue Naturstoffe aus marinen Mikroorganismen und ihrer Interaktion mit der Umwelt. Enterprise Europe Network. EU Workshop 2010. "Investitionsbank Schleswig-Holstein/IB.Europa. Facharbeitsgruppe EU-Forschung." Kiel, 31.5.2010

Wiese, J.: Medizin aus dem Meer - Vom Standort zum Wirkstoff. Symposium NaT-Working Meeresforschung, Bad Segeberg, 3.2.2007

Assortment of press reports with KiWiZ background

DIE WELT, 20.2.2006, Marine Arzneimittelforschung in Deutschland

WELT AM SONNTAG, 26.2.2006, Apotheke auf dem Meeresgrund: Schwämme, Muscheln und Mikroorganismen liefern neuartige Wirkstoffe für die Medizin. Erst ein Bruchteil ist erforscht.

DIE WELT, 27.2.2006, Medikamente aus dem Meer.

Wissen schafft Arbeit. Broschüre des Ministeriums für Wissenschaft und Verkehr des Landes Schleswig-Holstein, 10.3.2006, Marine Wirkstoff-Forschung – Das Meer als Quelle für neue Medikamente.

MARE-Magazin, 4/2006, Zuckertang stoppt Juckreiz. Die Meere sind sie als biologische Apotheke en vogue. In den Tiefen fahnden Forscher nach neuen Substanzen gegen Krebs und andere Krankheiten. Als potenzielle Wirkstoff-Lieferanten gelten vor allem Mikroorganismen oder Schwämme.

Kieler Hochschulzeitung „unizeit“, 8.4.2006, Meeresapotheke. Schmerzmittel aus Meeresschnecken, Krebsmedikamente aus Schwämmen – marine Organismen produzieren Stoffe mit Arzneiwirkung. Das neu gegründete Zentrum für marine Wirkstoffforschung am IFM-GEOMAR erforscht ihr Wirkspektrum.

MARE-Magazin, No. 56, Juni/Juli 2006, Meer als Apotheke. Ozeane sind ein unerschöpfliches Reservoir für Wirkstoffe gegen Krebs, Entzündungen, Viren oder Pflanzenschutz.

Geoscience – Magazin für Geo- und Naturwissenschaften, Juli 2006, Arzneistoffe aus dem Meer: Marine Mikroorganismen liefern Wirkstoffe für neuartige Therapeutika.

Münchner Merkur, No. 182, 9.8.2006, Gesundheit & Wissen, Medizin aus dem Meer. Forscher suchen nach neuen Wirkstoffen.

Broschüre des Ministeriums für Wissenschaft, Wirtschaft und Verkehr des Landes Schleswig-Holstein, August 2006, Exzellente Forschung – Exklusive Firmen.

Broschüre des Ministeriums für Wissenschaft, Wirtschaft und Verkehr des Landes Schleswig-Holstein, September 2006, Initiative Zukunft Meer,

Kieler Nachrichten, 23.1.07, Medikamente aus dem Meer. Bakterien und Pilze auf wirksame Substanzen für die Medizin erforschen. Eröffnung der neuen Räumlichkeiten in Kiel-Wyk.

Financial Times, 20.6.07, Tauchgang auf Schatzsuche: Medizin aus dem Meer,

Leibniz-Journal, Oktober 2007, „Erforschung der biologischen Rolle von Wirkstoffen in den natürlichen Lebensgemeinschaften und in der Entwicklung neuer Wirksubstanzen zu Produkten für die pharmazeutische und medizinische Anwendung“, in: „Pharmakologische Wirkstoffe“ von Brigitte Stahl-Busse.

EUROPA-Report 2007/Nr. 114, Zentrum für Marine Wirkstoffe in Kiel: Marine Mikroorganismen als Ressourcen für die Biotechnologie.

Kieler Nachrichten, 16.11.07, Eröffnung Biotech-Center Kiel.

Ministerium für Wissenschaft, Wirtschaft und Verkehr des Landes Schleswig-Holstein, Wiemker, R. (ed.), p. 19-21, Dez. 2007, Das Kieler Wirkstoffzentrum: Initiative Zukunft Meer.

Maritimes Jahrbuch Schleswig-Holstein 2007/2008, Wirkstoffe aus dem Meer – Chancen für neue Medikamente. Zukunft Meer.

Life Science Nord, Ausgabe 1/2008, Gemeinsamer Firmenauftritt: Planton, Proteo und KiWiZ bündeln Kompetenzen.

Bioforum, 31. Jahrgang, Februar 2008, Blaue Biotechnologie auf dem Vormarsch. Neue Wirkstoffe aus Meeresorganismen.

Apotheken-Umschau, Wort und Bild Verlag, Baierbrunn. Mai 2008, Medizin aus dem Meer.

LABOR & MORE, Mai 2008, Das Meer als Schatztruhe neuer Wirkstoffe.

Kieler Nachrichten, 4.2.2009, Die Stadt hat ihr eigenes Bakterium. Neues Bakterium nach Kiel benannt: Kiloniella laminariae. Entdeckung von „*Kiloniella laminariae*“ durch Kieler Mikrobiologen gilt als kleine wissenschaftliche Sensation.

DIE WELT, 3.2.2009: Bakterium nach Kiel benannt: *Kiloniella laminariae* (dpa/lno) Mikrobiologen haben in der Ostsee vor Kiel ein neues Bakterium entdeckt und es nach der Stadt Kiel *Kiloniella laminariae* benannt.

Lübecker Nachrichten, 4.2.2009: Bakterium nach Kiel benannt: *Kiloniella laminariae*. Mikrobiologen haben in der Ostsee vor Kiel ein neues Bakterium entdeckt und es nach der Stadt *Kiloniella laminariae* benannt.

SanderMielke.de, Die digitale Heimatzeitung für Ostholstein, 4.2.2009, *Kiloniella laminariae*: Landeshauptstadt gratuliert Kieler Forschern. Mit großer Freude haben Kiels Oberbürgermeisterin Angelika Volquartz und Stadtpräsidentin Cathy Kietzer die Entdeckung des bisher unbekannten Bakteriums *Kiloniella laminariae* in der Ostsee vor Kiel aufgenommen. „Wir gratulieren den Mikrobiologen vom Kieler Wirkstoffzentrum am IFM-GEOMAR zu diesem sensationellen Erfolg.

Uetersener Nachrichten, 3.2.2009, Bakterium nach Kiel benannt: *Kiloniella laminariae*. Mikrobiologen haben in der Ostsee vor Kiel ein neues Bakterium entdeckt und es nach der Stadt Kiloniella laminariae benannt.

TAZ, 4.2.2009,´*Kiloniella laminariae*, Bakterium. Die Abwehrkämpfer.

Schleswig-Holsteinischer Zeitungsverlag, 3.2.2009, Gestatten, wir heißen "Kiel". Forscher des Kieler IFM-Geomar haben in der Ostsee ein neues Bakterium entdeckt und es "Kiel" getauft. Vielleicht könnte es bald als Antibiotikum eingesetzt werden.

Hamburger Abendblatt, 1. 2.2009 „Ostsee vor Kiel ein bisher unbekanntes Bakterium entdeckt und es „Kiloniella laminariae“ getauft, teilte das Institut am Dienstag mit…“,

Life Science Nord, 1/2009 „Reinsubstanzbibliothek mariner Naturstoffe: Wirkstoffe aus dem Meer neu geordnet“.

Kieler Nachrichten, 15.4.2009, Kieler Wirkstoffzentrum wird ausgezeichnet für Arznei aus dem Meer als „ausgewählter Ort im Land der Ideen“.

Kieler Nachrichten, 18.5.2009, Kieler Wirkstoff-Zentrum bot als „Ort der Ideen“ Einblicke. Wie entstehen Medikamente aus dem Meer? Spannende Einblicke in ein zukunftsweisendes Forschungsfeld bot am Sonnabend das Kieler Wirkstoff-Zentrum beim Tag der offenen Tür. Es wurde im Rahmen der bundesweiten Kampagne als „Ort der Ideen“ ausgezeichnet.

NORD-OSTSEE-REPORT, 16.05.2009, Medikamente aus dem Meer, Mit einem Tag der offenen Tür präsentiert sich ab 10.00 Uhr das Kieler Wirkstoffzentrum (KiWiZ) am Leibnitz-Institut für Meereswissenschaften (IFM-Geomar). Hier können Besucher einen Einblick in die Forschung an Wirkstoffen aus dem Meer erhalten.

KIELER EXPRESS, 25.7.2009, Medikamente aus dem Meer: Kieler Wirkstoffzentrum KiWiZ erforscht Mikroorganismen.

Kieler Nachrichten, 8.10.2009, „Auch die Biotech-Branche spürt die Krise“. - Das Kieler Wirkstoff-Zentrum präsentiert sich und seine Methoden auf der BIOTECHNICA 2009, der größten europäischen Fachmesse.

Medizin Aspekte, 15.6.2010.Marine Biotechnologie Norddeutschlands vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Pressebox, 15.6.2010, Marine Biotechnologie Norddeutschlands vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Dpa, 15.6.2010, Norddeutschlands Marine Biotechnologie vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Uni-Protokolle, 15.6.2010, Marine Biotechnologie Norddeutschlands vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Informationsdienst Wissenschaft (idw), 15.6.2010, Marine Biotechnologie Norddeutschlands vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Kieler Nachrichten, 15.6.2010, Norddeutschlands Marine Biotechnologie vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Ostsee-Zeitung, 15.6.2010, Norddeutschlands Marine Biotechnologie vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Schweriner Volkszeitung, 15.6.2010, Norddeutschlands Marine Biotechnologie vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Segeberger Zeitung, 15.6.2010, Norddeutschlands Marine Biotechnologie vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Norddeutsche Neueste Nachrichten, 16.6.2010, Norddeutschlands Marine Biotechnologie vernetzt sich. Gründungsversammlung eines Nordverbunds am IFM-GEOMAR.

Schleswig-Holsteinische Landeszeitung, 16.6.2010, Netzwerk für die marine Biotechnologie.

Neues Deutschland, Berlin, 30.4.2011, Aus dem Meer auf den Acker: Kieler Forscher fahnden bei Mikroben in den Ozeanen nach Pflanzenschutzmitteln.

Kieler Nachrichten, 26.5.2011, Forscher wollen Krebs mit Meerespilzen bekämpfen.

Informationsdienst Wissenschaft, 25.5.2011, Meerespilze für mehr Gesundheit. EU-Projekt zur Gewinnung mariner Wirkstoffe startet in Kiel.

Forum für Wissenschaft, Industrie und Wirtschaft, 25.5.2011, Meerespilze für mehr Gesundheit. EU-Projekt zur Gewinnung mariner Wirkstoffe startet in Kiel Innovations-Report.

Tauchjournal, Abtauchen im Netz, 26.5.2011, Meerespilze für mehr Gesundheit. EU-Projekt zur Gewinnung mariner Wirkstoffe startet in Kiel.

Life Science Nord, 1/2011, Ostsee unter internationaler Lupe, Das Projekt »Submariner« ist gestartet.

Auf dem Weg zurück zur Natur, Frühjahr 2011, Flur und Furche.

Kieler Nachrichten, 10.5.2012, Blaue Biotechnologie sieht rosarot.

Radio & TV Interviews

Imhoff, J.F.: Apotheke Meer. Das Atlantische Aspirin. MARE Radio Sondersendung, 6.3.2006

Imhoff, J.F. and Wahl, M.: Marine Botenstoffe. Interviews. Bayrischer Rundfunk, 6.3.2006

Wiese, J. und Imhoff, J.F.: MARE Radio, Interview vom 11.12.06

Imhoff, J.F.: Eröffnung KiWiZ, N3, 22.1.2007

Imhoff, J.F.: Medizin aus dem Meer: Ostseereport, 6.5.2007, 18.00 Uhr, N3

Imhoff, J.F.: Produkte aus dem Meer, N3, 13.5.2007

Imhoff, J.F.: Neues aus dem Meer, N3, 13.6.2007

Imhoff, J.F., Wahl, M,: "Marine Wirkstoffe": Beitrag für 3SAT/nano

Imhoff, J.F:: „Marine Medizin“ beim Schweizer Fernsehen

Imhoff, J.F.: InWaterTec, N3, 22.10.2007

Imhoff, J.F.: Eröffnung Biotech-Center Kiel, N3, 15.11.2007

Imhoff, J.F.: Interview ZDF, 21.2.2008

Imhoff, J.F.: Neues Bakterium nach Kiel benannt: *Kiloniella laminariae*. NDR, Schleswig-Holstein-Magazin, 4.2.2009

Stöhr, R., Walhorn, M., Imhoff, J.F. (2011) Reportage für „Die Durchblicker“ über das KiWiZ. Sendedatum 6.5.2011 NDR Info

Presentations on Expositions

Fairs

BIOTECHNICA 2008: KiWiZ presents research strategies for early phases of drug development from habitat to hit candidate on Germans largest biotechnology exhibition, Gemeinsamer Ausstellungsstand mit Life Science Nord, Hannover, 7.-10.10.2008

BIOTECHNICA 2009: KiWiZ presents research strategies for early phases of drug development from habitat to hit candidate on Germans largest biotechnology exhibition, Gemeinsamer Ausstellungsstand mit Life Science Nord, Hannover, 6.-8.10.2009

Husum Messe "Innovationen zum Begreifen – Made in Schleswig-Holstein" 18.1.2012: touch screen slide show on „Marine Natural Products“ and show case „Das Meer als Apotheke“

Analytica 2012: Efficiency and material protection of a new cell disruption method for the extraction of bioactives from algae, bacteria and fungi. München, Germany, 19.-20.4.2012

Achema 2012: Genome based methods for the exploration of natural products from marine fungi for the treatment of cancer. Frankfurt, Germany, 19.6.2012

Exhibitions

Exhibition ship „MS-Wissenschaft zum Jahr der Gesundheit“, 19.5.–29.9.2011: corporate video of KiWiZ, touch screen slide show on „Marine Natural Products“ and show case „Das Meer als Apotheke“.

Exhibition on „Schätze der Tiefsee“ im Ozeaneum Stralsund (open since 19.8.2011): A show case on „Apotheke Meer“

11. Münchener Wissenschaftstage 22.-25.10.2011: touch screen slide show on „Marine Natural Products“, and show case „Das Meer als Apotheke“

Promotion Material

Corporate video „Medizin aus dem Meer: Das Kieler Wirkstoff-Zentrum KiWiZ“ (http://www.geomar.de/index.php?id=filme)

Touch screen slide show and interactive touch screen

Show box “Wie der Brotkrumenschwamm in die Apotheke kommt: Medizin aus dem Meer”.

Flyer “New Natural Products from Marine Microorganisms - Blue Biotech from Kiel”

The first word bacteria (a *Streptomyces* isolate) in KiWiZ can write.

Imprint

KiWiZ, the Kiel Center for Marine Natural Products at the Helmholtz Centre for Ocean Research GEOMAR: A research platform for marine natural product research and biotechnology

Text & Layout: Johannes F. Imhoff, Antje Labes, Jutta Wiese

Photos provided by the authors, KiWiZ, GEOMAR and Rolf Schmaljohann

Publisher: Johannes F. Imhoff, Antje Labes, Jutta Wiese

Printed by hansadruck Kiel on PRIMASET, FSC Mix Credit

Sponsored by MicrobiMaris Biotech GmbH

www.kiwiz.org, Am Kiel-Kanal 44, 24106 Kiel

Kiel, first print July 2012, second revised print October 2012

Photo back cover: Colonies of *Aureobasidium pullulans* on an agar plate