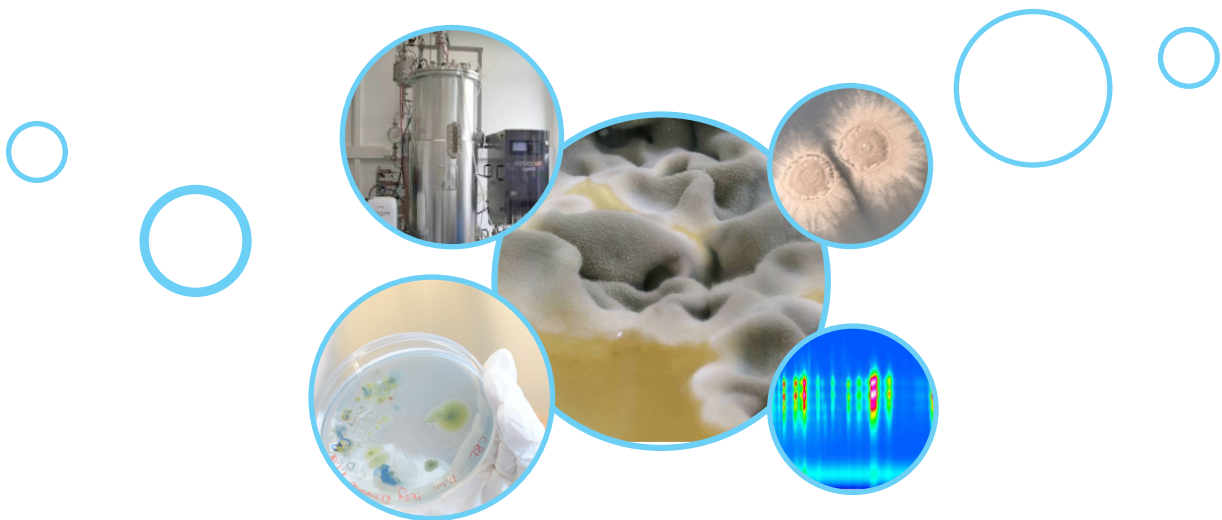


Blue Biotechnology Cooperation Event New Strategies and Future Perspectives

9–10 May 2012, Kiel, Germany

Programme & Abstracts



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www.submariner-project.eu

Venues & Map



Agenda of Day 1: Wednesday, 9 May 2012

- 08:45–09:30 Registration
- 09:30–09:45** **Welcome** by Cordelia Andreßen, State Secretary, Ministry of Science, Economic Affairs and Transport of Land Schleswig Holstein
- 09:45–09:55** **Welcome** by Hinrich Habeck, Norgenta North German Life Science Agency
- 09:55–10:05** **Welcome** by Johannes F. Imhoff, GEOMAR | Helmholtz Centre for Ocean Research Kiel
- 10:05–10:15** **Brief introduction to the SUBMARINER project**
Angela Schultz-Zehden, s.Pro – sustainable projects

STATE-OF-THE-ART AND FUTURE PERSPECTIVES OF BLUE BIOTECHNOLOGY

Chair: Joanna Przedzrymirska, The Maritime Institute in Gdansk, Poland

- 10:15–11:00** **Keynote: Marine Biotechnology opportunities and challenges – Are we realizing the vision and strategy for Europe?**
Jan-Bart Calewaert, Marine Board at the European Science Foundation, Belgium
- 11:00–11:15 **Blue Biotechnology all around the Baltic Sea**
Jutta Wiese, GEOMAR | Helmholtz Centre for Ocean Research Kiel, Germany
- 11:15–11:35 Coffee break
- 11:35–13:30 **STATE-OF-THE-ART AND FUTURE PERSPECTIVES OF BLUE BIOTECHNOLOGY IN THE BALTIC SEA REGION COUNTRIES:**
- 11:35–11:50: Denmark**
Torger Børresen, DTU Food, Denmark
- 11:50–12:05: Latvia**
Juris Vanags, Association of Biotechnology of Latvia
- 12:05–12:20: Finland**
Päivi Tammela, University of Helsinki, Finland
- 12:20–12:35: Sweden**
Henrik Pavia, University of Gothenburg, Sweden
- 12:35–12:50: Germany**
Johannes F. Imhoff, GEOMAR | Helmholtz Centre for Ocean Research Kiel, Germany
- 12:50–13:05: Lithuania**
Vytas Rimkus, SPILA, UAB, Lithuania
- 13:05–13:20: Poland**
Alicja Kosakowska & Adam Żak, Institute of Oceanology, Polish Academy of Sciences
- 13:20–13:30: Summary**
- 13:30–14:30 Lunch break

BLUE BIOTECHNOLOGY – SCIENCE MEETS INDUSTRY

14:30–15:10 **Keynote: Biotechnological advances in discovery and biosynthesis of bioactive secondary metabolites in marine microalgae**
Allan Cembella, Alfred Wegener Institute, Germany

15:10–16:10 **SUB-SESSION GENETICS**
Chair: Thomas Frahm, Norgenta North German Life Science Agency, Germany

15:10–15:25: Knowledge capture mechanisms studies as a tool to facilitate European Blue Biotech analysis
Daniel Pardo, CNRS/MNHN, France

15:25–15:40: Marine functional genomics
Antje Gardebrecht, University of Greifswald, Germany

15:40–15:55: Fungi associated to mediterranean seagrasses and algae: diversity ecological role and potential exploitation
Giovanna Cristina Varese, University of Turin, Italy

15:55–16:10: Knowledge transfer from environmental genomic science to marine biotechnology – big data, big challenges
Johanna B. Wesnigk, EMPA, Germany

16:10–16:45 Coffee break

16:45–17:30 **SUB-SESSION FOOD**
Chair: Levent Piker, CRM – Coastal Research & Management, Germany

16:45–17:00: Analysis of fish cell powder from *in vitro* cultured cells
Marina Gebert, Fraunhofer Research Institution for Marine Biotechnology (EMB), Germany

17:00–17:15: Production of omega-3 fatty acids by algae
Kristian Spilling, Finnish Environment Institute (SYKE), Finland

17:15–17:30: Healthy appetite for Algae: Milk products containing algae
Marie Shrestha, ttz Bremerhaven, Germany

18:00–20:00 **Poster Session**
Aquarium Kiel at GEOMAR (entrance on the seaside)
Düsternbrooker Weg 20
DE–24105 Kiel

20:00 Conference Dinner
Restaurant “Schöne Aussichten”
Düsternbrooker Weg 16
DE–24105 Kiel

Please note: registered participants only, limited capacities

Agenda of Day 2: Thursday, 10 May 2012

BLUE BIOTECHNOLOGY – SCIENCE MEETS INDUSTRY (CONTINUED)

08:45–09:15 SUB-SESSION COSMETICS

Chair: Antje Labes, Kieler Wirkstoff-Zentrum (KiWiZ) am GEOMAR, Germany

08:45–09:00: From sustainably cultivated seaweed to certified organic cosmetics – the brand “Oceanwell” as a success story for a value-added chain originating from ecologically farmed marine resources
Inez Linke, oceanBASIS GmbH, Germany

09:00–09:15: Sulfated polysaccharides of *Delesseria sanguinea*: Pharmacological activities indicating anti-inflammatory and anti-skin aging effects
Juliane Grimm, University of Kiel, Germany

09:15–12:15 SUB-SESSION PHARMACEUTICALS

Chair: Daniel Pardo, CNRS/MNHN, France

09:15–10:00: *Keynote*: Marine biodiversity as source of new anticancer compounds. The experience of PharmaMar
Fernando de la Calle, PharmaMar, Spain

10:00–10:15: Marine microorganisms – a promising source for novel therapeutics
Sabine Mundt, University of Greifswald, Germany

10:15–10:30: AAC – Algae Against Cancer: Preliminary data of a national research project
Marion Zenthöfer, CRM, Germany

10:30–11:00: Coffee break

11:00–11:15: Integrated analytical approaches towards marine natural products discovery
Thomas Ostenfeld Larsen, DTU, Denmark

11:15–11:30: SeaLife Pharma – the discovery of novel pharmaceutical lead compounds by innovative strategies
Alexander Pretsch, SeaLife Pharma, Austria

11:30–11:45: Hamacanthins from deep-water marine sponge as lead for the development of anti-cancer drugs
Christian Peifer, University of Kiel, Germany

11:45–12:00: Aquapharm – Commercial development of blue biotechnology
Andrew Mearns Spragg, Aquapharm Biodiscovery Ltd, United Kingdom

12:00–12:15: Genome based methods for the exploration of natural products from marine fungi for the treatment of cancer
Antje Labes, Kieler Wirkstoff-Zentrum (KiWiZ) am GEOMAR, Germany

12:30–13:15 Concluding Panel discussion

Panelists: Torger Børresen (DTU Food, Denmark), Jan-Bart Calewaert (Marine Board at the European Science Foundation), Fernando de la Calle (PharmaMar, Spain), Allan Cembella (Alfred Wegener Institute, Germany), Steffen Lüsse (Ministry of Science, Economic Affairs and Transport of Land Schleswig-Holstein, Germany), Juris Vanags (Association of Biotechnology of Latvia)
Moderation: Angela Schultz-Zehden, s.Pro – sustainable projects

State-of-the-art and future perspectives of Blue Biotechnology

Keynote:

Marine Biotechnology opportunities and challenges – Are we realizing the vision and strategy for Europe?

Jan-Bart Calewaert

Marine Board at the European Science Foundation, Belgium

The interest of the scientific community, and to a lesser extent of industry, in marine biotechnology has grown rapidly in the past decade owing to a recognition of the sheer scale of opportunity presented by the largely unexplored and unexploited biodiversity of our seas and oceans and the need to meet growing demands that cannot be satisfied from terrestrial sources alone. Several publications (e.g. from Marine Board-ESF, European Commission CWG and EU-US Task Force on Biotechnology) have highlighted the importance of marine biotechnology and its potential to make a significant contribution to sustainable development on all fronts, including social, economic and environmental. However, it is only since recently that a concerted effort is being made in Europe to develop an initiative that seeks to take action on many of the issues identified, to improve the coordination of marine biotechnology research, raise its profile, and

contribute to the establishment of the Knowledge Based BioEconomy (KBBE).

This presentation will sketch key policy developments of European marine biotechnology in the last decade, highlight areas of progress and address future perspectives. It will present some of the main opportunities and challenges identified by strategic exercises and assess where we are in realizing the vision and strategy for Europe proposed in Marine Board Position Paper 15 on Marine Biotechnology. Finally, the presentation will highlight some of the outcomes of the FP7 CSA MARINEBIOTECH project (www.marinebiotech.eu), in particular the preliminary results of the mapping of European Marine Biotechnology Research landscape being conducted by Marine Board-ESF.

Jan-Bart Calewaert



Jan-Bart has a background in bio-engineering (Ghent University, Belgium) and ecological marine management (University of Antwerp and Free University of Brussels). He has been involved in many marine science coordination and support activities often at the interface between science and policy, combining his broad expertise in marine sciences with his knowledge of the marine and maritime policy landscape in Belgium and Europe. At the Marine Board, Jan-Bart coordinates the Board's foresight, policy and project activities in various working areas such as marine biotechnology, oceans and human health, climate change impacts on the marine environment and marine pollution.

Blue Biotechnology all around the Baltic Sea

Jutta Wiese

GEOMAR | Helmholtz Centre for Ocean Research Kiel, Germany

The SUBMARINER project seeks to turn the Baltic Sea into a model region by fostering sustainable economic development and improved environmental conditions through new maritime products and technologies. In this project the Centre for Marine Natural Products (KiWiZ) at GEOMAR focuses on aspects of Blue Biotechnology. The aim is to assess the state of the art and perspectives of Blue Biotechnology of all countries around the Baltic Sea, to evaluate further applications and to define technical requirements taking into account environmental aspects, legal

regulations and economic aspects. This study will characterise the future potential of marine resources for blue biotechnology and will work out major obstacles to the further development of this field. Promising scientific approaches and case studies of companies working in the discovery and/or economical exploitation of resources from the Baltic Sea will be presented. Among these resources are raw materials, valuable ingredients such as bioactive compounds, fatty acids, enzymes, biopolymers as well as genetic resources for biotechnological applications in phar-

maceutical industry, medical products, human diet, animal feed, cosmetic, wellness sector or bioremediation. All activities in this field aim to enhance the awareness in the public and in the scientific community, to improve human and environmental health as well as to increase economic benefits. The first results from

the SWOT (Strengths, Weakness, Opportunities, Threats) analysis clearly demonstrate the high potential of Blue Biotechnology for the BSR. The ultimate hope is to strengthen the Baltic Sea Region's competitiveness in Blue Biotechnology and to contribute to a sustainable development of the Baltic Sea Region.

Six priorities proposed for marine biotechnology in Denmark

Torger Børresen
DTU Food, Denmark

A survey initiated by the Ministry of Food, Agriculture and Fisheries in 2010 resulted in six priorities for the development of marine biotechnology in Denmark. Business opportunities were suggested and some elements for a successful strategy were proposed. The six priorities are the following:

- Increased exploitation of marine biomass. In addition to traditional fisheries, full utilisation of all catches and improved utilisation of by-products are suggested. Further, new species of fish and macro algae should be harvested.
- New farming operations. Aquaculture should be applied in its widest sense. Marine farming has the advantage that it does not impact freshwater resources. If established on land, water should be re-circulated and production limited to high priced species.
- Healthy diet. Marine fatty acids, proteins, peptides and micronutrients are found in large quantities in marine organ-

isms and should be contained directly or indirectly in the human diet.

- Discovery of new compounds, materials and biological activities. The large variation of marine organisms and the occurrence under extreme living conditions increase the chances for new commercial viable discoveries.
- Extraction of valuable biochemical components. Complex structures with special properties can be included in pharmaceutical products, cosmetics and special foods.
- Biofilm – from ships over the food industry to the interior of the human body. Biofilm is a deposit and growth of organisms on surfaces, usually with consequences unwanted for economical or health reasons.

The trends of Biotechnology in Latvia

Juris Vanags
Association of Biotechnology of Latvia

Latvian Biotechnology association (LBA) was created as the first Latvian biotech network in 2006.

The main aim of the LBA is to promote the development of biotechnology in Latvia by clustering of academia, governmental bodies and industry in joint projects, by participation in the international projects, by joint representation of their members in meetings and exhibitions, by promoting of education of young specialist in biotechnology and related fields, and by rising of public awareness on biotechnology in the society. LBA is a member of European Federation of Biotechnology and ScanBalt network.

The activities of Latvian Biotech SME, which use biotechnological methods in manufacturing and service, are oriented to the following directions:

1. The medical and pharmaceutical biotechnology;
2. The ecological biotechnological;
3. The design and manufacturing of the biotechnological equipments;
4. The Industrial biotechnology.

The biggest turnover is in the direction of the biotechnological equipments (different laboratory equipment, as well laboratory and pilot scale bioreactors), although the amount of companies are relatively small, they have the international recognition. Now research institutions and companies consider the opportunities to start activities in directions of blue biotechnology. As the first steps is the adaptation of methods used by potential partners of EU countries.

Finland: MAREX (EU FP7 Project): Exploring marine resources for bioactive compounds – From discovery to sustainable production and industrial applications

Päivi Tammela, Paula Kiuru, Tiina Lipiäinen, Jari Yli-Kauhaluoma & Heikki Vuorela
Faculty of Pharmacy, University of Helsinki, Finland

Through close co-operation between industrial and academic partners, EU FP7 project MAREX (www.marex.fi) will collect, isolate and classify marine organisms, such as micro- and macroalgae, cyanobacteria, sea anemones, tunicates and fish from the Atlantic, Pacific and Indian Oceans as well as from the Mediterranean, Baltic and Arabian Seas. MAREX is a joint effort of 19 academic, research institute, and industrial partners from 13 countries.

Extracts of marine organisms will be studied for several therapeutically and industrially significant biological activities, including anticancer, anti-inflammatory, antiviral and anticoagulant activities by applying a wide variety of screening tools. Furthermore, chromatographic isolation of bioactive compounds will be followed by structural determination. Sustainable cultivation methods for promising organisms and biotechnological processes

for selected bioactive compounds will be developed, as well as biosensors for monitoring the production of target compounds and food quality. The work will entail sustainable organic synthesis of selected active compounds and new derivatives, and development of selected hits to lead compounds. Attention will be paid to evaluate the overall feasibility of MAREX innovations for industrial product development in order to improve the sustainability and productivity of European marine biotechnology. Key issues of MAREX include better understanding of environmentally conscious sourcing of biotechnology products from the oceans, and increasing public awareness of marine biodiversity and potential. Finally, MAREX aims to offer novel marine-based lead compounds for European industry to strengthen their product portfolios related to pharmaceutical, nutraceutical, cosmetic, agrochemical, material and biosensor applications.

Blue Biotechnology in Sweden

Henrik Pavia
University of Gothenburg, Sweden

Blue Biotechnology in Germany – the Centre of Marine Natural Products Kiel

Johannes Imhoff

GEOMAR | Helmholtz Centre for Ocean Research Kiel, Germany

The local study on “Zukunft Meer” in Schleswig-Holstein in 2004 and the ESF report on Marine Biotechnology in 2010 both highlight the extraordinary importance of developments of blue biotechnology in the local and the European context.

There are a number of small companies dealing with products as resources of the ocean but only few activities of research activities in Northern Germany considering aspects of blue biotechnology of which the Centre of Marine Natural Products (Kieler Wirkstoff-Zentrum KiWiZ am GEOMAR) is the most prominent. This centre was founded in 2005 and substantially supported by the local Government in Kiel from 2005-2010. Major goals of the KiWiZ are the research on marine microbial resources, in particular bioactive marine natural products and their pro-

motion to application. In the first years, major achievements could be made due to the concerted efforts on microbial cultivation and diversity analysis, the establishment and maintenance of large culture collections of marine fungi and marine bacteria, a large set of first stage bioactivity assays, identification and chemical structure analysis of natural products and finally fermentation capacities for the experimental and the pilot stage. A library of pure marine natural products has been established, which is offered to interested partners. Among the new natural products identified such with antibiotic and antitumoral activities were dominant. From a financial point of view the perspectives appear critical, but from a scientific point of view, the potential is quite promising and the KiWiZ could develop to a model institution for blue biotechnology elsewhere.

Blue Biotechnology in Lithuania

Vytas Rimkus

SPILA UAB, Lithuania

Mostly people knows that algae grows in oceans, seas and also lakes. There are more than 30 000 species of algae which have been around billions of years. Spirulina is a blue-green microalgae naturally thriving in alkaline lakes is the most concentrated and nutritious whole food known to science.

Over few hundred scientific studies and clinical trials indicate health benefits associated with the use of Spirulina. Spirulina is the perfect multinutrient food for people of all ages and lifestyles who want a whole food source of vitamins and other nutrients.

SPILA, UAB took over much scientific work done by number of international scientists in field of human nutrition and animal productivity and economical efficiency. Areas of trials were Spirulina for diary cows, use for poultry, pig, carp fish and bees.

Understanding this we created natural preservation and digestion enhancement Spirulina based product on maximum nutrient preservation and without thermal preservation thus suitable

for vegetarians and everyone from children to elderly senior. As it represented unique combinations which were not used before it was internationally patented.

For animal nutrition our task was increase benefits for use natural Spirulina additive versus synthetic or chemical animal productivity enhancer. Main task group was milking cows. It is a classical and true example how it works. Result was a significant increase in cows milk yield and other benefits resulting net 50% –400% return per day investment on our new SPILAMIX product. This is hard to match analogue in this industry.

As Spirulina represents hundreds of different forms of nutrients as whole system of its interaction it is a great object of further studies of understanding what further benefits it can give for human and animal to enhance utilization its further use in many applications also as a source of vital elements.

Co-operation in patent sharing internationally and further product development is a main business objective for our company.

Blue Biotechnology in Poland

Alicja Kosakowska & Adam Żak

Institute of Oceanology, Polish Academy of Sciences, Poland

Blue biotechnology is dynamically developing branch of science. Application of molecular biology methods to marine and freshwater organisms is a worldwide trend which could lead to new important discoveries. This modern approach brings many opportunities along with possible practical applications and benefits for human medicine, pharmacy and industry.

The main goal of this presentation is to introduce and describe some of the scientific institutions in Poland that are involved in blue biotechnology. Presented information will cover research projects and future perspectives.

Blue Biotechnology – Science meets Industry

Keynote:

Biotechnological advances in discovery and biosynthesis of bioactive secondary metabolites in marine microalgae

Allan D. Cembella

Alfred Wegener Institute for Polar and Marine Research, Bremerhaven, Germany

Eukaryotic microalgae have been extensively studied for biotechnological applications but the pharmaceutical potential of bioactive compounds of marine species has scarcely been explored. This is in spite of the fact that >120 species of marine eukaryotic microalgae are known to produce bioactive metabolites, with potent toxic and/or other allelochemical properties, including against predators and competitors in marine ecosystems. These allelochemical interactions thus provide a plausible discovery and screening approach for novel bioactive metabolites, including insights into mode of action – the “chemical ecology strategy”. The known bioactive compounds comprise a wide diversity of metabolite groups, from linear and polycyclic ethers (e.g., brevetoxins) to tetrahydropurine alkaloids (e.g., saxitoxin) and secondary amino acids (e.g., domoic acid). Certain bioactive metabolites produced by marine dinoflagellates are shared with cyanobacteria (e.g. saxitoxin analogues) and similar non-riboso-

mal peptide synthases (NRPS) and polyketide synthase (PKS) genes have been identified. The relative simplicity of the cyanobacteria genome can thus provide model systems for genomic studies of biosynthetic genes from much more complex marine dinoflagellate genomes. An effective strategy for discovery and screening for bioactives from marine microalgae integrates classical natural products chemistry (LC-M/MS, NMR) with genomic and gene expression aspects, including high-throughput (next-generation 454)-sequencing and application of DNA microarrays, in laboratory cultures and field assemblages containing bioactive-producing taxa. Marine microalgae are attractive candidates for biotechnological exploitation because they are amenable to isolation and scale-up for mass culture for optimal yield of bioactives. Furthermore, taxonomic gene probes and gene expression platforms have been developed for several groups of eukaryotic microalgae and associated bioactive gene pathways.

Allan Douglas Cembella



Prof. Dr. Allan Douglas Cembella did his PhD at University of British Columbia, Vancouver, Canada at the Departments of Botany and Oceanography. Today, after numerous research stays all around the world, he is professor in the faculty of Natural Sciences at the University of Bremen and section head for Ecological Chemistry at the Alfred Wegener Institute for Polar and Marine Research, Bremerhaven, Germany. Since early days, one main focus of his research has been algae. Today, his research interests also include chemical and molecular ecology of protists as well as genetics, biochemistry, toxinology and ecotoxicology of harmful microalgae. Furthermore, Prof. Cembella is active in the fields of marine microbial biotechnology. The AWI Biosciences Division provides relevant expertise and facilities for marine biotechnology, with key competences in isolation and culture of marine microorganisms, isolation and structural elucidation of marine natural products, and bioactivity and allelochemical interactions.

Sub-Session Genetics

Knowledge capture mechanisms studies as a tool to facilitate European Blue Biotech analysis

Daniel Pardo¹, **Sophie Arnaud-Haond**², **Jesus M. Arrieta**³ & **Antoine Schoen**⁴

¹ CNRS/MNHN, France

² Ifremer, France

³ CSIC-UIB, Spain

⁴ Paris Est ,France

Knowledge Capture Mechanisms (KCM) are very similar to “Allosteric reaction” involving different parameters, control and feedback control. Analysis of KCM, at the core of technology transfer, contributes to a better understanding of interactions between University and Industry, Technology and Knowledge. The present communication is focused on KCM involving Marine Genetic Resources and results obtained by Sophie Arnaud-Haond et al. It will present a research project and preliminary results describing some examples of knowledge transfer pathways.

References:

Arnaud-Haond S, Arrieta JM, Duarte CM (2011) Marine Biodiversity and Gene Patents. *Science* 331: 1521-1522.

Arrieta JM, Arnaud-Haond S, Duarte CM (2010) What lies underneath: conserving the oceans' genetic resources. *Proc Natl Acad Sci U S A* 107: 18318-18324.

Marine functional genomics

Antje Gardebrecht

University of Greifswald & Institute of Marine Biotechnology, Germany

Facing the fact that to date most microorganisms remain uncultured, deep metagenome sequencing is indispensable to get an impression of microbial diversity and physiological potential in a natural habitat. Depending on large specific genome data sets, functional approaches such as metaproteomics have been applied to characterize the dynamic range of in situ expressed genes. Starting with a simple microbial assemblage as the symbiosis of deep-sea tubeworms and sulfide-oxidizing bacteria, we targeted on whole proteomes to resolve functional variations between monospecific bacteria residing in two different hosts.

Challenged by rapid advances in MS/MS-based technologies, we furthermore made an attempt to investigate complex microbial

communities in marine surface waters. Functional genomics allowed to directly link bacteria with metabolic and biogeochemical processes in the North Sea by identification of proteomic biomarkers. Future analyses of model organisms grown with habitat-specific substrates or being exposed to different stress- and limitation factors should give a more detailed picture of key proteins in marine systems. In this context, several visualization concepts are used to compare expression patterns of such individual marker genes under defined environmental conditions. Novel identified proteins of unknown function are finally characterized and exploited in respect to new biotechnological applications.

Fungi associated to mediterranean seagrasses and algae: diversity ecological role and potential exploitation

Giovanna Cristina Varese

University of Turin, Italy

Marine fungi play important ecological roles and represent a large source of novel metabolites and enzymes but remain one of the most under-explored group of organisms in the marine environment.

The aim of this study was to isolate and identify fungi associated with the seagrass *Posidonia oceanica*, the green alga *Flabellia petiolata* and the brown alga *Padina pavonia* and to screen them for the production of enzymes and secondary metabolites of pharmaceutical interest. The sampling was conducted in March

2010 in 2 sites of the Elba Island (Italy).

Hundreds of marine fungi were isolated and identified. Most of them belong to Ascomycota and represent saprotrophic species, some, in analogy to what happens in terrestrial habitats, could be symbionts of algae or seagrasses or parasite of plants and marine animals.

About one hundred strains were grown at different salt concentrations and tested for laccases, peroxidases and tannase activ-

ity and screened for the presence of polyketide synthase (PKS) genes and for their antimicrobial activity toward one pathogenic bacterium, four pathogenic yeasts and two algae involved in zoonotic disease.

The obtained results suggest that marine Ascomycetes are good producers of oxidative enzymes and tannases and hence can play an important ecological role in the decomposition of ligno-

cellulosic matrixes in the marine environment and can also be exploited for the production of these enzymes for different biotechnological purposes.

The molecular screening showed that 48% of the fungal strains resulted positive for the presence of PKS genes and many of them displayed a strong antibacterial, antifungal and/or anti-algal activity.

Knowledge transfer from environmental genomic science to marine biotechnology – big data, big challenges

Johanna B. Wesnigk
EMPA, Germany

Genomic sequence data are increasing exponentially also for marine organisms and metagenomic data sets. These include information for novel functions and promising variety of known and utilised enzymes. While costs for the sequencing are decreasing, it still constitutes a major effort to obtain and maintain samples. Therefore cooperation between science and industry is necessary.

Several EU-funded projects address how to facilitate access to data, samples and expertise. A dedicated focus on knowledge transfer to industry is provided by the CSA project “Marine Genomics for Users”, which deals with training, a knowledge output database and with establishing direct contacts between genomic scientists and marine biotechnologists. Several elements of this knowledge transfer strategy will be illustrated in this talk and a short overview on related projects and their outputs given.

Furthermore, the emerging large collaborative project Micro B3 “Marine Biodiversity, Bioinformatics and Biotechnology” will be presented. It concentrates on integrating genetic and ecological information in one open-access system for linking (meta)genomic prediction to ecosystem biology and to biotechnological aspects. Related training will focus on bioinformatic needs by these two user groups, including also governance and IPR aspects.

The ultimate objective is to learn from marine diversity - from fishing bio-active molecules to cultivating organisms and maybe soon synthesizing genes - to decipher and apply novel functions found in the marine environment.

Sub-Session Food

Analysis of fish cell powder from *in vitro* cultured cells

Marina Gebert
Fraunhofer Research Institution for Marine Biotechnology (EMB), Germany

Seafood is considered to be important for a healthy diet, as it contains valuable proteins and high quality fats. Especially oily fish such as tuna, herring, trout or salmon contain large amounts of highly unsaturated omega-3 fatty acids - in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These have been proven to be beneficial for human health.

However, natural fish sources face two major problems: fish stocks continuously decrease and heavy metals accumulate in fat tissue of fishes along the food chain. Thus, the exploitation of novel sources for omega-3 fatty acids is ever gaining more importance.

We investigated the ability of a highly proliferative *in vitro* fish cell culture from Sturgeon larvae (*Acipenser oxyrinchus*) estab-

lished in our laboratory to produce nutraceutical grade omega-3 fatty acids. We found out that these cells convert short chain polyunsaturated fatty acids into long chain highly unsaturated fatty acids. An increase of the total amount of EPA and DHA could be achieved by the addition of α -linolenic acid (ALA) to the cell culture and the subsequent reduction of cell culture temperature. However, an industrial production is not yet feasible, as *in vitro* culturing of large quantities of anchorage dependent cells is currently cost-intensive. Thus, one of the main challenges is to develop new bioreactors with large surfaces suitable for fish cell culture, which allow cost-effective production of cell biomass to enable access to fish derived products with low ecological damage.

Production of omega-3 fatty acids by algae

Kristian Spilling¹, Jukka Seppälä¹, Niklas Virkkala¹, Susanna Nenonen¹, Elina Salo¹, Katarina Natunen¹, Timo Tamminen¹, Dagmar Enss² & Heiko Rischer²

¹ Finnish Environment Institute – SYKE, Finland

² VTT, Technical Research Centre of Finland

Algae can contain high amounts of essential fatty acids (EFAs) that organisms at other trophic levels have limited abilities to synthesize. This has led to a lot of attention to algae as a potential feed for aquaculture and as raw material for the nutraceutical industry.

Omega-3 fatty acids, in particular Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) have known health benefits to humans and these fatty acids are produced in various amounts by algae. In order to find what algae would be best suitable for EPA and DHA production, we screened 20 different algal species, belonging to 4 different phyla, for their fatty acid composition in both exponential and stationary (N-limited) growth phase.

Diatoms contained the highest EPA concentrations whereas dinoflagellates and haptophytes were high in DHA. Green algae and cyanobacteria contained very little of either EPA or DHA (with the exception of *Dunaliella salina* that contained some

EPA). Generally, both EPA and DHA content increased in stationary growth phase. The highest EPA producer was *Thalassiosira baltica* (3.4 % of DW) and most DHA was found in *Scrippsiella hangoei* (9.7 % of DW).

In a separate experiment the effect of different nutrient limitation (N and P limitation) was studied in the diatom *Phaeodactylum tricornutum* and the haptophyte *Isochrysis galbana*. The total lipid concentration was highest during N limitation; however, the EPA content in *P. tricornutum* and DHA content in *I. galbana* was highest during P limitation, 9.2% EPA and 8.7% DHA of DW respectively.

The results suggest that some algae can contain high amounts of omega-3 fatty acids (up to 10% of DW), but the production is highly phyla- or species-specific. The main omega-3 fatty acids produced was either EPA or DHA, but not at the same time. Different stress situations (e.g. nutrient limitation) increased the overall omega-3 concentration, but species specific optimizing should be carried out before any production starts.

Healthy appetite for Algae: Milk products containing algae

Marie Shrestha

ttz Bremerhaven, Food Technology & Bioprocess Engineering, Bremerhaven, Germany

In Asia, algae are well-known food products since decades. In Germany food products based on algae are rare: algae are mostly used in pharmaceutical and cosmetic industries. However algae are rich in vitamins, minerals, trace elements and fibre and at the same time contain low fat. Raising the popularity of food products containing algae would contribute to a general improvement in health. Therefore curd and cream cheese products were enriched with brown algae for people with nutritive deficiencies.

Germany is an iodine-deficient country and supplementation of iodine therefore needs to take place through enriched food products. However whilst an iodine deficiency interferes with

the thyroid function, too high iodine consumption also has harmful health effects. A thorough formulation of dairy products with algae was therefore performed. The macroalgae were homogenized and dried under mild conditions and incorporated in dairy recipes to have a positive influence on the taste, texture and appearance of the products.

Consumers' acceptance and willingness to buy were determined: 60 men and women between 20 and 65 years of age rated curd cheese products containing algae in a blind test. The acceptance towards the innovative algae food products was good.

Sub-Session Cosmetics

From sustainably cultivated seaweed to certified organic cosmetics – the brand “Oceanwell” as a success story for a value-added chain originating from ecologically farmed marine resources

Inez Linke

oceanBASIS GmbH, Germany

The company oceanBASIS farms the sugarkelp *Saccharina latissima* in an integrative sustainable aquaculture facility in Kiel Fjord and specialises in extracting marine-based natural substances for health and beauty products.

Marine biologists cultivate young algae on seeding ropes in the laboratory. After about 8 weeks they are launched in the open-water farm and grow about half a year in fresh seawater. After harvesting the fresh algae are fermented to an alcoholic extract rich in active marine ingredients such as minerals, iodine, special algae sugars and polyphenols.

Based on this unique extract and natural seawater oceanBASIS developed the organic cosmetics brand “Oceanwell” which was certified and launched in 2009.

Clinical studies revealed, that Oceanwell has a beneficial skin-compatible effect. Thus it is suitable especially for dry and sensitive skin. Moreover Oceanwell invigorates, regenerates, energises and protects the skin in a natural way. Oceanwell is distributed in Germany via natural cosmetics shops, perfumeries and spas and the own internet shop. Export has started recently first to China, now to the USA.

After 7 years of research oceanBASIS invented a new cosmetic ingredient, oceanic collagen, extracted from jellyfish. Studies revealed unique high waterbinding capacity. The organically certified cosmetic ProAge Line “OceanCollagen” was developed specially for demanding skin.

Sulfated polysaccharides of *Delesseria sanguinea*: Pharmacological activities indicating anti-inflammatory and anti-skin aging effects

Juliane Grimm, Inken Groth & Susanne Alban

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Delesseria sanguinea (Hudson) Lamouroux (D.s.), the dominating red macro-alga occurring at an artificial large-scale reef in the Baltic Sea, (Nienhagen, Germany), contains sulfated polysaccharides (SP). As known from heparin, SP exhibit not only anticoagulant, but a wide range of biological activities. The aim of the study was to examine the activity profile of these alga-derived SP (D.s.-SP).

Performing the standardized water-extraction with 13 algae batches, harvested over two years, the D.s.-SP showed to be of reproducible high quality. The biological effects of D.s.-SP were compared with unfractionated heparin (UFH) in various *in vitro* test systems recording relevant steps within the (patho-)physiological network of inflammation, metastasis, and haemostasis: (1) elastase- and (2) hyaluronidase- activity assays, (3) haemolytic complement modulation assay (CMA), (4) the tumor cell adhesion to P-selectin assay, further the coagulation assays (5) activated partial thrombin time (APTT) and (6) thrombin time

(TT), and finally, the cytotoxicity assays (7) with 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and (8) lactate dehydrogenase (LDH). All tests were performed at least three times on different days.

Compared to UFH, the D.s.-SP revealed to be superior in all the assays except for APTT and TT. Cytotoxicity studies with tumor and human blood cells showed no negative effects on cell viability.

Regarding the selected effects, discussed to contribute to anti-inflammatory and antimetastatic activity (1-4), the D.s.-SP were shown to be superior to UFH. In contrast, they were less anticoagulant, which may indicate a reduced risk to induce bleeding.

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Sub-Session Pharmaceuticals

Keynote:

Marine biodiversity as source of new anticancer compounds. The experience of PharmaMar

Fernando de la Calle
PharmaMar, Spain

Traditionally, higher plants and terrestrial microorganisms have proven to be the richest sources of natural drugs. However, we are living in a planet of oceans. The marine ecosystem covers more than 70% of the earth's surface but represents 95% of the biosphere. The first living organisms appeared in the sea more than 3,500 million years ago and evolutionary development has equipped many marine organisms with the appropriate mechanisms to survive, developing exquisitely complex biological and chemical mechanisms for defence, attack, signalization and other still unknown purposes. These biological capabilities are clearly revealed by their ability to biosynthesize and release potent chemical weapons that are active per se.

Such novel chemical structures often result in new modes of action and open up the potential of new ways to treat cancer and other diseases. The current scientific, academic and biotech-pharmaceutical industries have recognized this opportu-

nity and thousands of bioactive compounds are being discovered and some of them are being testing in clinical trials, mainly in oncology. But the conversion of a bioactive molecule into a medicine is a long and risky process. It involves astronomic investment for developing the identification and validation of new targets, drug discovery, medicinal chemistry and drug delivery, apart from ensuring the future supply, where chemical synthesis and biotechnology are the preferred sources for manufacturing.

PharmaMar, founded in 1986, is a biopharmaceutical company devoted to the discovery and development of novel cancer drugs derived from marine organisms. In addition to Yondelis, the PharmaMar's first marketed product which was launched in October 2007 in EU for the treatment of soft tissue sarcomas and in July 2009 for some types of ovarian cancer, the company also has 5 marine derived products in clinical trials and a large pipeline of potential new drugs.

Fernando de la Calle



Executive MBA and Ph.D in Molecular Microbiology at the University Autónoma de Madrid. He joined PharmaMar in 1988. Since 1999, he has had been Head of the Marine Microbiology R&D Department. The activities of his research group are focused on the study of the marine microorganisms as potential producers of antitumor compounds and the design of biotechnological processes to supply drug substances. He is one of the authors of the current manufacturing process of Yondelis, a marine derived compound recently approved by the EMEA for the treatment of soft- tissue sarcomas (2007) and recurrent ovarian cancer in combination with Caelyx® (2009). Currently, he is the Principal Investigator by PharmaMar in three funded EU projects related to blue biotechnology: MAMBA; MicroB3 and MaCuMBA.

Marine microorganisms – a promising source for novel therapeutics

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Worldwide marine organisms, especially microorganisms such as fungi, bacteria and cyanobacteria, are recognized as sources for novel natural products. In 2010 more than 1000 new structures with a wide range of bioactivities have been published.¹⁻²

The focus of research in our group is the bioassay-guided isolation and characterization of active compounds produced by marine fungi and cyanobacteria. Novel secondary metabolites from marine fungi from Red Sea mangrove drift wood³ or from drift-wood, collected from the Baltic Sea⁴, exhibit in vitro antibacte-

rial activity to *Staphylococcus* strains including MRSA and anti-viral activity to Influenza A and Herpes simplex viruses respectively. An endophytic fungus from red alga *Gracilaria* sp., collected from Indonesian coast, produces substances inhibiting growth of a phytopathogenic fungus⁵. From cultivated Vietnamese cyanobacteria polyketides with strong cytotoxic activity to tumor cell lines were isolated⁶. A *Lyngbya* strain was the source of antibacterial and cytotoxic active cyclic undecapeptides⁷ and from the *Anabaena* strain Bio 33, obtained from the Baltic Sea, cyclic antifungal lipopeptides are in characterization.

Besides the isolation of pure active compounds we use whole biomass of marine microorganisms to prepare microparticles by Maresome-technology.⁸ It could be shown that microparticles from the biomass of Bio 33 called Bio33-Maresome® inhibit dermal colonization of different MRSA strains and even of the VRSA MU50 strain. A prophylactic skin care with Bio33-Maresome® to prevent nosocomial infections has been developed.

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AAC – Algae Against Cancer: Preliminary data of a national research project

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⁴ Christian Albrechts University Kiel, Institute of Pharmacy, Germany

⁵ Source BioScience Ltd., Germany

⁶ LipoFIT Analytic GmbH, Germany

Based on previous studies, demonstrating significant inhibitory effects on proliferation of tumor cells triggered by various extracts of different macroalgae, a national research network will now enlighten structure and mechanisms of action of potent ingredients of marine algae. In the project “Algae Against Cancer” (AAC), funded by the Federal Ministry of Research and Education (BMBF), three private and three university partners investigate cellular responses upon treatment with algae-derived extracts. Possible synergistic effects of a combined action of several substances will be analyzed with innovative methods of genomics and metabolome analysis.

Preliminary results from studies with different hematologic and solid tumor cell lines are presented showing patterns of i) inhibition of cell proliferation, ii) alterations in gene expression profiles, iii) metabolic response, and iv) inhibition of target enzymes. The first results suggest a real chance, i) for specifying substances that have not yet been described as cancer therapeutics, ii) for the identification of structural modifications of already known drugs leading to improved anti-tumor activity, and iii) for describing previously unknown mechanisms of action of known algal ingredients.

Integrated analytical approaches towards marine natural products discovery

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Many strategies can be followed in discovering novel drugs from microbial sources. We have demonstrated that phenotypic based microbial taxonomy can be a successful path to microbial drug discovery¹. This involves the use of multivariate methods for clustering and selection of talented strains for testing in various bioassays (e.g. antimicrobial, anticancer). The second step in the discovery process is **dereplication**, where we use *state-of-the-art* high resolution mass spectrometry (<1 ppm mass accuracy and accurate isotope pattern) in combination

with comprehensive compound databases in order to ensure not to waste time isolating and elucidating the structures of already known compounds². When likely unknown compounds have been identified an explorative solid-phase extraction approach³ is applied for micro-scale fractionation on a set of different types of columns (RP, ion-exchange, size, NP), in order to determine more chemical properties of the bioactive(s). This further aids selection of a fast optimal purification strategy towards the pure bioactives prior to NMR characterization.

We will illustrate our integrated analytical approaches and highlight some of the results that we have gained in a recent larger Danish biodiscovery project focusing on marine bacteria⁴⁻⁶, as well as some of our future challenges in determining the chemistry of microalgae and marine derived fungi.

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- ⁶ We acknowledge support from the Programme Committee for Food, Health and Welfare under the Danish Strategic Research Council.

SeaLife Pharma – the discovery of novel pharmaceutical lead compounds by innovative strategies

Alexander Pretsch
SeaLife Pharma, Austria

SeaLife Pharma is an innovative biotech company with the focus on the discovery and development of novel bioactive compounds. Therefore the company developed different methods and strategies to higher the hit-rate. In the talk Dr. Pretsch will talk a little bit about the research and development strategy of the company, including their different screening platforms in the anti-infective, anticancer and neurodegenerative field. The innovative Ecotargeting approach or the “silent gene story”

should be delighted. With actual examples Dr. Pretsch will show the hard way from the discovery to the identification of a real lead structure and development candidate. Every step is illustrated by data and results of the Sealife Pharma research and development, and should give a short overview in the field of marine drug discovery and development in an interior country like Austria.

Hamacanthins from deep-water marine sponge as lead for the development of anti-cancer drugs

Christian Peifer
Christian Albrechts University Kiel, Germany

Marine-derived bioactive compounds and their novel chemical scaffolds have been shown to be interesting starting points for drug discovery programs. In this study we report on the marine sponge alkaloids Hamacanthins as lead for the development of potent ATP competitive protein kinase inhibitors with implications as anti-cancer drugs. Initially, we identified the pyrazin-2(1H)-one scaffold of Hamacanthins by Molecular Modeling studies to be able to bind in the ATP pocket of receptor tyrosine kinases (RTK), a validated drug target family for the treatment of various neoplastic diseases. In order to enhance potency and selectivity of this compound class, structure-based design stud-

ies on human RTK were performed, suggesting straight forward lead optimization strategies. Accordingly, we focused on a Medicinal Chemistry project to develop pyrazin-2(1H)-ones as optimized RTK binders. In order to reveal Structure-Activity-Relationships, we established a novel flexible synthetic route via microwave mediated ring closure towards asymmetric 3,5-substituted pyrazin-2(1H)-ones and produced a set of novel compounds. Herein, we identified highly potent RTK inhibitors with IC₅₀ values in the nM range which have interesting properties for their further development towards anti-cancer drugs.

Aquapharm – Commercial development of Blue Biotechnology

Andrew Mearns Spragg

Aquapharm Biodiscovery Ltd, United Kingdom

Over the last 20 years, the pharmaceutical industry has seen a decrease in discovery and success based on computational and combinatorial chemistry, and an increase in base costs imposed by increasing regulatory requirements and a higher rate of failures during the development process. Couple this to the potential of structural, hence intellectual property overlap between libraries of synthetic compounds and the need for low-cost, scalable and chemically unique new scaffolds, the pharmaceutical industry is starting to re-evaluate the potential of natural products to provide the industry with new drug leads. Aquapharm is a marine biotechnology company pioneering the development of untapped and drug-like chemical diversity derived from a proprietary collection of over 9,000 marine micro-organisms. Due to the fundamental limitations of accessing the full range of chemical productivity produced from micro-organisms (marine or terrestrial) many of which are present in “cryptic” / or locked away biosynthetic pathways, Aquapharm has developed a novel approach of modulating the microbial metabolome to unlock the bio-synthetic potential of micro-organisms

for the discovery of new compounds – many of which are capable of modulating hard to drug protein:protein drug targets. This is our SeaRch™ platform which leverages IP initially filed in 2007 on techniques to achieve the reactivation of cryptic secondary metabolite pathways in micro-organisms via epigenetic remodeling in response to the induction of oxidative stress. Aquapharm has utilized this technology to screen 1100 marine strains from our collection for the discovery of novel antibiotic and anti-inflammatory compounds with our partners AMRI based near Seattle. Preliminary data has demonstrated that this has been a great success and has yielded a substantial number of novel pharmacophoric scaffolds, many of which are below 500m/z and fall well within the Lipinski rules for drug like chemistry. Further screening of some of these novel drug-like compounds against a broad range of GPCRs, enzymes & ion channels has discovered chemistry that is highly potent and also highly specific against interesting and complex drug targets reading onto CNS & oncology.

Genome based methods for the exploration of natural products from marine fungi for the treatment of cancer

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Kieler Wirkstoff-Zentrum (KiWiZ) am GEOMAR, Germany

Despite marine fungi are a potent group of secondary metabolite producers, they are not well characterised and underutilised in terms biotechnological application. Here, we demonstrate the sustainable exploitation of marine natural resources providing appropriate culture conditions for the group of marine fungi, thus enabling efficient production of marine natural products in the laboratory and also in large scale cultures, avoiding harm to the natural environment. In the focus are new anti-cancer compounds. Beside isolation of new fungal strains from unique marine habitats, the molecular development of effective producer strains is in the focus. Genomes of selected candidate strains

originating from our unique strain collection of marine fungi are characterised with respect to secondary metabolite production. This knowledge is use to optimise production using molecular methods.

This approach is an outcome of the project “MARINE FUNGI” within the KBBE framework of EU’s FP7. We develop a process concept for these compounds providing the technological basis for a sustainable use of marine microbial products as result of “Blue Biotech”.

Poster Abstracts

Quantitative population-epigenetics in screening and development of biologically active compounds from marine organisms

1 Reinhold Stauß
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This publication propounds to render screening and development of biologically active compounds from marine organisms for scientific research and biotechnological applications more efficient by taking into account laws of inheritance. The argument undertakes to show that statistical (epi-) genetic theory as a basis for developing screening methods may be appropriated with the same facility as is done in plant and animal breeding schemes. The research discipline and the treatment subject are the same for both the breeder and the investigator of biologically active agents, save each treats different sides of the same coin (organism). The breeder endeavours to improve the genotype -- for him environments are 'fixed' effects; the "environmentalist" is not able to augment the genotype -- one strives to intervene in the environment by effecting a specific phenotypic expression with a biologically active compounds within the 'norm of reaction' inherent in the genotype.

Likewise index selection based on statistical epigenetic theory can be used to improve efficiency in screening compounds for potential to enhance quantitative agricultural characters such as yield, stability and resistance to unfavourable environmental influences (e.g., water stress, cold temperatures, disease resistance) – as well indeed, for potential in pharmacological intervention.

Ecological and Evolutionary Epigenetics is a new field of frontier research at the intersection between molecular genetics and evolutionary ecology. The term 'Epigenetics' is used only for about ten years. The statistical Quantitative Population-Epigenetics theory was published with STAUSS, R., 1992: Genetic analogues in chemical screening. *Zeitschrift für Pflanzenkrankheiten und Pflanzenschutz, Stuttgart, 99(6), 653–656* and STAUSS, R., 2012: *Quantitative population-epigenetics in screening and development of regulator-active compounds. Julius-Kühn-Archiv, 434, 589–585.*

Potential of aquaculture slong a salinity gradient in the German western Baltic Sea

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The considerable potential of the German Baltic Sea aquaculture which has been studied and explored in past years is in apparent contrast to the small number and size of the existing commercial aquaculture facilities.

With support of "Deutsche Bundesstiftung Umwelt" (DBU) we were able to develop opportunities for integrated aquaculture in the Western Baltic Sea in a three year project. In particular, the potential for extractive marine aquaculture of *Mytilus edulis* and *Saccharina latissima* was observed at different locations along the German western Baltic coast using production yields of mussels and seaweed, and environmental conditions as site selection criteria.

As the hydrographical conditions varied between the locations, biomass production and condition indices of the observed organisms showed related patterns. Maximum algae growth rates

were observed in April 2011 at the trout farm in the Kiel Fjord, lowest growth rates were encountered in December 2010 in Eckernförde. Furthermore, seaweed growth rate increased with available light at most stations, but was almost constantly high at the farm site in the Kiel Fjord throughout the observation period. Mussels grew well at all locations, however highest condition indices were noted in autumn 2010 and lowest in early spring 2011.

The high growth rates of the observed organisms suggest that aquaculture of the Western Baltic coast has a great potential. Eckernförde Bay and parts of Kiel Fjord are registered shellfish waters, thus mussel farming is possible from the legal as well as from the biological and probably also from an economical point of view.

μaqua

3 Ulrich Breitenbach
MariLim GmbH, Germany

Monitoring the quality of drinking water is of paramount importance for public health. "Water is not a commercial product but a heritage that must be protected, defended and treated as such" (Water Framework Directive 2000/60/EC). The threat of waterborne diseases in Europe will predictably increase in the future as the human population increases and as a result of globalization and migration from non-EU countries and of climate change. Development of efficient, sensitive, robust, rapid and inexpensive tests to monitor various aspects of water quality represents an essential milestone within the strategy for control and prevention of diseases caused by waterborne pathogens and by algal toxins. Traditional methods for the detection of waterborne pathogens, based on cultivation, biochemical characterisation and microscopic detection are laborious and time-consuming; molecular biological tools have now greatly enhanced our ability to investigate biodiversity by identifying species and to estimate gene flow and distribution of species in

time and space. μAQUA aims to design and develop a universal microarray chip for the high-throughput detection in water of known and emerging pathogens (bacteria, viruses, protozoa and cyanobacteria) and to assess the water quality monitoring the presence of select bioindicators (i.e. diatoms). A chip able to detect cyanobacterial toxins will also be developed. These innovative molecular tools should be amenable to automation so that they could be deployed on moorings for routine semi-continuous monitoring of water quality. μAQUA also aims to identify cyanophages potentially capable of controlling and mitigating the periodical blooming of toxic cyanobacteria in drinking water reservoirs. Overall, these innovative and cost efficient technologies will reduce energy requirements and improve performance of water treatment, and allow rapid management response to new situations brought about by environmental (including climatic) changes.

Development of a miniaturised screening-method for fungal mutants with enhanced production of specific natural compounds

4 Annemarie Kramer¹, Linda Paun², Antje Labes¹, Frank Kempken² & Johannes F. Imhoff¹
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Fungi are well known as good producers of natural compounds. However, the potential of marine fungi to produce bioactive compounds is under investigated. To improve this knowledge, the EU-project MARINE FUNGI (EU FP/, 265926) has set its focus on the isolation and characterisation of new anticancer compounds from marine fungi. To improve the production of the compounds or even to change the compound spectra diverse methods are used within the project.

One good example for the enormous potential of marine fungi is a *Scopulariopsis brevicaulis* isolated from the marine sponge *Tethya aurantium*. The strain produces the cyclodepsipeptides scopularide A and B¹ and was selected for a molecular optimisation process using random mutagenesis by UV radiation. A challenge during this molecular optimisation process is the handling

of the huge number of mutants, whose secondary metabolites are not easily detected, as eg. by visual control or antibiotic activity determination. Hence, the specification of the secondary metabolites of each mutant strain is still a time and material consuming step. Therefore, a miniaturised screening method was developed. The established method covers a decreased cultivation volume, a fast extraction method and an optimised LC-MS analysis format. With this method a remarkable time reduction could be achieved and in addition a reduction of process deviation, important for the comparability of the screening results.

¹ Yu, Z.; Lang, G.; Kajahn, I.; Schmaljohann, R.; Imhoff, J. J. Nat. Prod. 2008, 71, 1052–1054

Marine fungi: a rich source for natural products

5 Johanna Silber, Birgit Ohlendorf, Arlette Erhard, Antje Labes & Johannes F. Imhoff
Centre for Marine Natural Products (KiWiZ) at GEOMAR, Germany

The Wadden Sea is a unique habitat since it underlies permanent changes due to the tidal influence. Fungi living in such an environment presumably need a high metabolic versatility in order to survive. As metabolic versatility may also relate to natural product biosynthesis, fungal strains isolated from the German Wadden Sea were investigated with regard to secondary metabolite production. The 109 strains isolated from sediments

were grown under varying culture conditions, in shaken or static cultures and in different media. Cultures were extracted applying liquid-liquid extraction, and extracts were analysed by HPLC-DAD/MS. One of the fungal strains showed exceptionally attractive metabolite profiles and was selected for detailed investigations. The structures of the purified compounds of this strain were elucidated by NMR spectroscopy. Beside the known

substances triclinononic acid (Bashyal and Gunatilaka, 2010), 6-hydroxymellein, 6-methoxymellein (Dunn et al. 1979), orbuticin, 32-hydroxyorbuticin, antibiotic 15G256 α -2, 15G256 β -2 and 15G256 π (Schlingmann et al. 2002), six new compounds were

identified. Part of these substances exhibited strong antibacterial and cytotoxic properties in bioactivity assays and hence could have a potential in biotechnological applications.

Emulsifiers from *Ascophyllum nodosum*

6 K. Petersen & H. Steckel
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Emulsions – in liquid or semisolid state – are important dosage forms for cosmetic and pharmaceutical use. They are composed of a hydrophilic and a lipophilic phase and, therefore, need to be stabilised by surface-active substances. For the stabilisation of emulsions polymeric emulsifiers can be used, that can form a film at the phase boundary layer and often also increase the viscosity of the coherent phase. Known polymeric emulsifiers are for example hydrophobically derivatised carbomers or substituted cellulose ethers.

In this work, aqueous extracts containing sulphated polysaccharides (fucoindanes) from *Ascophyllum nodosum* were analysed for their potential emulsifying properties. Fucoindanes already showed beneficial properties like antioxidant or anti-inflammatory activity¹, so the combination of pharmaceutical and technological use is desirable.

As model lipophilic phase middlechain triglycerides in an amount of 5% to 25% (m/m) were used. The hydrophilic phase

only consisted of aqueous extract from *Ascophyllum nodosum* and to slow down the creaming velocity, polyacrylic acid was added as gelling agent without own emulsifying capacity. The emulsions were preserved with benzyl alcohol.

Preparation of the emulsions was performed by high pressure homogenisation and their stability was analysed by a light backscattering technique. A digital microscope was used to get impressions of the homogeneity of the emulsions.

In conclusion, aqueous extract from *Ascophyllum nodosum* is suitable for the stabilisation of emulsions, as long as the viscosity is enhanced by another suitable substance.

¹ Bo Li et al., Fucoindan: Structure and Bioactivity; Molecules 2008, 13, 1671-1695

The draft genome of marine isolate of *Scopulariopsis brevicaulis* using three different next generation sequencing methods

7 Abhishek Kumar & Frank Kempken
Christian Albrecht University of Kiel, Germany

There are several hundreds of marine fungi species are known and they possess unique features in the fungal diversity, as they have to adopt marine environment. The enormous biodiversity of marine fungi is mirrored by the molecular diversity of their secondary metabolites¹. However, a very little is known about marine fungal genetic resources. Although several terrestrial habitat fungal genomes have been sequenced using Sanger sequencing in last two decades and recently, the *Sordaria macrospora* genomic sequences became available using next-generation sequencing². However, not a single genome of marine isolates of fungi is yet known. To further explore marine fungal diversity, we set out to sequence marine isolates of fungi. Here we report the first example, *Scopulariopsis brevicaulis*, which has previously been known as a common soil saprophyte and has been isolated from a wide variety of substrates. Some species of *Scopulariopsis* are reported to cause human diseases³. *S. brevicaulis* is also known to produce cyclic peptides scopularide A and B⁴.

We have established the draft genome of a marine isolate of *S. brevicaulis* using three different next-generation sequencing methods namely, roche 454, illumina and ion-torrent. Herein, we present our current results of *S. brevicaulis* assembled genome of about 32 Mb size using 726,314, 247,824,350 and

2,556,553 reads from roche 454, illumina and ion-torrent, respectively. We found the contig length is large for roche 454 (935 contigs/N50 – 88 kb) in comparison to contigs of illumina (29330 contigs/N50 – 1.7 kb) and ion-torrent (32008 contigs/N50 – 1.6 kb). Furthermore, we will provide results of gene family comparisons with respect to other fungi. This genome characterization assists mycologist to further carry out research with this species, which largely hindered due to unavailability of the genome.

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³ Cuenca-Estrella, et al. (2003). *Scopulariopsis brevicaulis*, a Fungal Pathogen Resistant to Broad-Spectrum Antifungal Agents. Antimicrobial Agents and Chemotherapy 47, 2339–41.

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Baltic Sea eelgrass *Zostera marina* L.: Potential use and paradigm change

8 **Christel Dötsch-Jutsch**
AQUAZOSTA® MB, Germany

AQUAZOSTA opens a new chapter in processing cast ashore seagrasses from the Baltic Sea. *Zostera marina* was used already for many centuries as an insulation and filling material. Nowadays, in coastal touristic areas, this marine raw material is handled as garbage or debris which has to be removed during beach cleaning in summer. Inadequate beach cleaning often results in illegal removal of sand from the beaches and deposition of the nature plant material.

Moreover, *Zostera marina*, the unique marine flowering plant is often included in scholarly works as seaweed (marine algae). Although in general, seaweeds are separated from seagrasses (eelgrass in Europe), there is often confusion because of purely existing knowledge and inexpert translation with far reaching consequences. E.g. in the NACE Rev. 2 2008 EU regulations, the marine eelgrass is classified as a plant from the woods.

A paradigm change is required regarding the processing of seagrasses which are washed ashore: Zosteraceae eelgrass are no algae or "seaweed", no garbage for deposits, for a combustion plant, no biomass for production of biogas and biofuel, like some macroalgae biomasses are.

Seagrass is an ecologically valuable marine nature resource for refinement by combined processing the value-added chain, from the start of collecting to the end of the production of patented (3 EP), biotechnologically manufactured innovative goods: cosmeceutical, pharmaceutical, nutraceutical, and technical products.

Beach cast natural resource *Zostera marina* with its botanical complex MAREZOSTIN® is a broad range raw material as it is not found in any other plant from the ocean.

Identification and profiling of marine fungi-derived anti cancer compounds using cell-based cytotoxicity assays and 3-D culture methods

9 **Jonas Weber**
European ScreeningPort GmbH, Germany

A group of ten worldwide partners are focussed on the identification of marine fungi-derived anti-cancer agents within the FP7 project MARINE FUNGI. In the project, the European Screening-Port (ESP) is responsible for the application of screening technologies to identify and profile novel compounds.

The approach chosen is based on profiling compound activity against the NCI60 panel of cell lines which represents 9 diverse cancer types. The readout used is luciferase-based measurements of growth inhibition and toxicity (Cell Titer-Glo, Promega Corp.). Experiments were performed in 384-well microtiter plates using an automated screening system (Cell Explorer, PerkinElmer Inc.). The application of a microcarrier-based automated cell culture techniques (Biolevitator™, Hamilton Bonaduz AG) was an integral part of the project. The evaluation of standard compound profiling experiments in both, standard cell culture (T175 flasks) and microcarrier (Cytodex 3® beads), was per-

formed to establish reproducibility and comparability. Activity profiles were generated and analysed. Additionally, cell line dependencies were evaluated including growth characteristics as well as compound response activity profiles.

The screening experiments showed significant comparability of both cell culture methods. Hence, findings give access to a simple and fast screening system to evaluate marine natural products in the NCI60 cancer cell line panel. This technology will increase the efficiency for finding marine-derived anti-cancer agents. Compounds identified so far, showed reproducible dose-response curves in up-to-now 8 cancer cell lines. Further profiling of identified hits will use High Content Screening assays to monitor specific events such as apoptosis. In later stages, xenograft mouse models will be used to confirm any in-vivo efficacy.

Diversity of two exopolysaccharides from cyanobacteria of the genus *Synechocystis*

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Cyanobacteria can synthesize exopolysaccharides (EPS) in various amounts and of high variability consisting of 2 - 9 different monosaccharides¹. Up till now only two amino sugars are known to occur in cyanobacterial EPS: N-acetyl-glucosamine and N-acetyl-galactosamine². Besides polysaccharides also proteins are mentioned to occur in ethanol-precipitated fractions of purified cyanobacterial cultivation media³.

For the first time we identified N-acetyl-fucosamine (2-acetylamido-2,6-dideoxy-D-galactose) as a component of the EPS of *Synechocystis aquatilis* SAG 90.79 (*S. aquatilis*). The monosaccharide composition of these EPS is very different from that of other known cyanobacteria². They mainly consist of only four sugars: fucose (42%), arabinose (34%), N-acetyl-fucosamine (17%) and glucose (1%). In addition, they contain about 20% of sulfate groups and are free of protein moieties. According to NMR analyses *S. aquatilis* seems to build up a polysaccharide with irregular arrangement of the monomer sugar units.

In contrast, the EPS of *Synechocystis pevalekii* SAG 91.79 (*S. pevalekii*) are rather comparable to other cyanobacterial EPS² and contain mannose (25%), glucose (19%), galactose (12%), fucose (10%), rhamnose (8%), xylose (8%), glucosamine (5%) and arabinose (3%). Most interesting is the additional occurrence of a remarkable amount of protein (~39%) with aspartic and glutamic acid as dominating amino acids.

Our results show the high heterogeneity of cyanobacterial exometabolites even within one genus.

¹ Bertocchi C et al. (1990) Arch Microbiol 150:558–563.

² De Philippis RS et al. (2001) J of Appl Phycol 13:293–299.

³ Kawaguchi T, Decho AW (2000) Prep Biochem Biotechnol 30 (4):321–330.

Marine biopolymer for tissue repair: Engineering cartilage on jellyfish collagen matrices

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In an aging community, defects in knee cartilage ending in knee replacements with artificial joints become a serious problem. A low-cost method to delay these severe intrusions is thus requested. We present a new material from a marine source for cartilage tissue engineering. Pure collagen from jellyfish *Rhopilema esculenta* is used to cast a porous, dry sponge. On this matrix, chondrocytes are seeded and implanted into a cartilage defect where they are thought to reproduce new hyaline cartilage.

Several matrices for MACI (matrix-induced chondrocyte implantation) were developed from bovine or porcine collagen, thus they all produce unwanted fibrous cartilage and bear the risk of passing diseases like BSE.

The new matrix from jellyfish collagen shows important advantages over other matrices. This collagen has similarities to vertebrate collagen-type II, the main type in healthy hyaline cartilage. Coming from an invertebrate, there is no risk of passing BSE or initiation of arthrosis by inflammation. Culture experiments with porcine chondrocytes showed a reproduction of hyaline cartilage, having a very high collagen-type II fraction. Additionally, stiffness of the matrix could be adjusted to aim a tissue-specific matrix. Porcine chondrocytes responded to varied stiffnesses with different collagen-type II and I patterns. On a less rigid matrix (2 kPa) chondrocytes preserved their phenotype better than on a stiffer matrix (20 kPa). This could be the fundament for engineering not only cartilage but also other tissues like skin or bone on the basis of jellyfish collagen.

High molecular weight antioxidative compounds from marine macroalgae

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Marine macroalgae produce a wealth of different compounds with antioxidative potentials. Particularly the superoxide scavenging activities of polysulphated polysaccharides from different sources have been investigated. Fucoidans are heat stable antioxidants, able to effectively scavenge superoxide anions. This is in addition to, and independent from their other effects, such as anti-coagulant activities. Different molecular fucoidan species with different superoxide-scavenging efficiency can be isolated with high yield, dependent on source material and purification method. Specific luminescence assays are employed

to reliably quantify their antioxidative activities. Pure and well characterized fucoidans may have the potential to serve many different pharmaceutical and clinical applications. They may, for example, alleviate inflammatory symptoms caused by the formation of superoxide. Current cooperative projects implicate the screening of macroalgae from the Baltic Sea for fucoidan abundance. Thereby molecular weight distributions, superoxide-scavenging activities, long-term stability, and optimisation of purification protocols are in the focus of our research.

Bioactive peptides produced by the cyanobacterium *Nodularia spumigena*

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Cyanobacteria are known to produce a wide diversity of secondary metabolites. Among the compounds both acute toxins and potential drug candidates have been reported. *Nodularia spumigena* is a filamentous cyanobacterium that occurs in many aquatic ecosystems worldwide. In the brackish water of the Baltic Sea, it temporarily accumulates into high biomass.

In the current work, structure and biological activity of non-ribosomal peptides produced by *N. spumigena*, were studied. Based on LC-MS/MS analyses, 44 compounds were characterized. Out of these, a linear peptides, spumigins (18) and aeruginosins (5) were shown to be the most abundant and most frequently occurring once. These peptides belong to strong inhibitors of trypsin, thrombin and other serine proteases. Addition-

ally, 2 hepatotoxic pentapeptides called nodularins and 19 cyclic hexapeptides classified to anabaenopeptins (nodulapeptins) were detected. The anabaenopeptins showed inhibitory activity in protein phosphatases and serine proteases assays.

In the work, the metabolic diversity of the Baltic *N. spumigena* strains was also compared. The analyses of 44 peptides in 8 isolates revealed that the Baltic population is not clonal and individual strains are characterized by different peptide profiles.

The results of the study showed that the bloom-forming *N. spumigena* is a rich source of peptides of potential pharmaceutical application.

Sustainable Alternative for fishmeal/fishoil in fishfeed

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The supply of ingredients (especially proteins and fatty acids) in fish feed is the bottleneck for the sustainable production of marine fish in aquafarms. In order to decrease the fishing pressure on natural fish stocks we present a sustainably produced alternative for fish meal/fish oil.

In an IMTA facility in Kiel Fjord algae and mussels are farmed. The environmental benefit of this system is the complete absence of emissions. The mussels are produced foremost for human consumption, while the unusable part of the production can be used for animal feeds.

Analysis showed that mussel meal is a very good provider for EPA and DHA, which are essential for the development of marine fishes.

Tests of various extraction methods revealed that the extraction of fat is not economic due to the relatively low total fat content (5–14% of DW) of blue mussels.

We measured degradation of PUFAs during storage, an effect which we assign to the exposure to air. Comparison of various processing techniques has shown that the most economic pro-

cedure is cooking, de-shelling, grinding and drying the mussel meat. This procedure does not damage the PUFA's when minimizing heat and air contact during the milling process.

First tests using mussel meal as attracting compound in fish feed showed a comparable acceptance by fish (turbot) compared to a fish meal additive

Mussel meal is not yet competitive with fish meal in an economic sense; however, we assume that within approx.10 years prices for mussel meal and fish meal will converge.

The future of Blue Biotechnology – Climate change and future perspectives of aquaculture in the German Baltic Sea coast

15 **Tim Staufenberger & Peter Krost**
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Climate change effects not only the terrestrial, but also the marine environment. The need for adaptation to a future climate regime is hence a necessity. Within the RA:dOST (Regional Adaptation Strategies for the German Baltic Sea Coast) project CRM (Coastal Research and Management, Kiel) elucidates the future potential of aquaculture within the Kiel Fjord. Due to the discharge of warm water from the Kiel power plant into the Kiel Fjord we have the unique opportunity to investigate the effects of elevated water temperatures already now in an existing envi-

ronmental system. This warm water input is presently used by a fish farm (Fischzucht Tassilo Jäger-Kleinicke). Furthermore the first German algal farm (courtesy of oceanBASIS) is operating in the Kiel Fjord. Both enterprises produce value products but how will climate change effect e.g. algae and fish? Based on observations made on these aquacultures and climate models we developed a concept to answer the arising question: What holds the future for aquaculture?

A novel concept for the simple and rapid quality control of sulfated polysaccharides of marine origin

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Sulfated polysaccharides (SP) from algae are of great interest since they have a broad spectrum of promising biological activities as well as they are obtained from non-animal, renewable resources.

The aim of this study was to establish a sensitive, simple and rapid assay, suitable for the quality control of SP by using exemplarily the SP from the red algae *Delesseria sanguinea* (Hudson) Lamouroux (D.s.-SP). This should be based on the recently developed fluorescence microplate assay using Polymer-H, a sensor molecule for direct quantification of sulfated glycans, whereby the fluorescence intensity (FI) of the Polymer-H was concentration-dependently amplified by D.s.-SP. As calibrator fondaparinux (3.75 µg/mL) and as reference a D.s.-SP-batch with a

high level of purity were used (7.5 µg/mL). By investigating 52 different D.s.-SP-batches, appropriate limits for their quality turned out to be 80–120% FI increase in the Polymer-H assay. In this way, it is possible to control both correct isolation procedure and stability of D.s.-SP. Furthermore, the FI results of the 52 batches showed a good correlation with their respective elastase inhibition activities (IC50). The combination of these two assays additionally allows the discrimination between D.s.-SP and other SP.

In conclusion, the presented sensor-based fluorescence assay is ready to use for simple and rapid identification and quality control of SP of marine origin.

Ocean Actives – extracts from marine organisms as active ingredients for the use in the cosmetic industry

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Ocean Actives means high-quality extracts from marine organisms. oceanBASIS develops and produces extracts from macro algae and jellyfish carefully respecting the environment.

Its expertise is the sustainable use of marine resources and the development of marine active ingredients for the skin and hair

care products industry. The certified extracts have excellent properties for the intensive care of stressed or sensitive skin: nourishing and stimulating trace elements from the sea, moisturizing algae sugars, powerful antioxidants, natural UV-protecting substances and jellyfish collagen with special properties for cosmetic and medical uses.

Biological activity of cyanobacterial secondary metabolites

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Secondary metabolites are organic compounds not directly involved in the normal growth, development and reproduction of organism. These compounds could be produced by plants, algae, fungi and microorganisms and potentially show biological activity. Metabolites which affects growth and development of biological and agricultural systems are called allelochemicals. Allelopathy is a natural phenomenon occurring in both terrestrial and aquatic environments. Allelopathins could increase or reduce growth of other organisms, cause different physiological effects in target organisms including cell death. The studies about secondary metabolites with allelopathic activity are important because of their possible influence on aquatic ecosystems and potential practical application in pharmacy, medicine, food science and other branches of industry.

The main concern of this work was to investigate the influence of cyanobacterial metabolites on growth of green algae and bacteria.

Experiments included laboratory samples and water samples from Baltic Sea. Cultures were provided on liquid medium to obtain the extracellular secretion. Cell-free solutions from cyanobacterial cultures and marine water were obtained by filtering through the glass-fiber filters. Samples were concentrated with nonionic resin and by evaporation. Biological activity was investigated on green algae and bacteria cultivated on liquid or solid medium.

Allelopathic effects of extracellular compounds towards green algae were observed. Both cyanobacterial and environmental samples demonstrated siderophore-like properties. We noticed bacteriostatic and bactericidal effects of studied samples.

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MicrobiMaris Biotec – Blue Biotech services from Kiel

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Within the development of marine natural products for a broad spectrum of application, a gap was identified between academia and market. Hence, during the establishment of the Kieler Wirkstoff-Zentrum as a network node for biotechnology of marine bioactives, a small enterprise was founded in order to valorise products of interest and commercialise services of Blue Biotech for customers in academia and industry: MicrobiMaris Biotec GmbH was founded in 2007 and attends to all aspects of marine biotechnology, including process development of microbial production and market implementation of new compounds from marine microbes. Development and commercialisation of

products of marine biotechnology is performed independently and together with partners.

MicrobiMaris Biotec accomplishes services for a broad range of microbiological and chemical analytics and other aspects of marine natural product development. In particular, services are offered for biotechnological and microbial process development, identification of microbes, analyses and identification of metabolites (especially bioactives) and execution of testing biological activities relevant to medical application and plant protection.

Analysis of the biodiversity in sea water from different oceans

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The BG BioTeQ is a training programme at Elly-Heuss-Knapp-Schule, a vocational college in Neumünster. The students are being qualified as technical assistant in biology and additionally acquire their Abitur (german university entrance diploma). The project group consists of first year students and started its work as part of the regular training in the school's laboratory in March 2012. The project aims to introduce methods of microbiological analysis to the students. The topic was chosen to relate the used methods to a relevant topic within the field of the debate on climate-protection. The increasing shipping traffic on the world's seas and oceans is spreading microbes and bacteria through ballast water. This causes a change in the water's original flora and

fauna. Climate connected parameters such as warming of the water etc. also contribute to this development. Analysis of the microbiological constituents of the different samples and comparison will provide information on their impact on each other. These findings can build a basis to develop countermeasures for the problem of "contaminated" ballast water. At the moment samples from the southern and eastern Baltic Sea, the southwest of the Atlantic Ocean, Kiel-Canal, the Sea of Marmara and the Black Sea are analyzed. The water samples are examined in terms of their pH-value, content of bacterial toxins, oxygen demand and their resistance regarding temperature, (UV-) light and salt.