BIOPROSP 2006

Tromsø Science Park Conference Centre
Tromsø, Norway
October 11th – 12th, 2006

Objectives of the symposium:

- Visualize activities and commercial opportunities in marine bioprospecting.
- Be a national meeting place for participants and collaborating partners within marine bioprospecting.

Program committee:

The MABIT program	Unn Sørum
University of Tromsø	Trond Ø. Jørgensen
University of Tromsø	Tor Haug
Fiskeriforskning	Inge W. Nilsen
NorInnova AS	Karl-Johan Jakola
NorInnova AS	Reidun Klykken
Marbank	Kjersti Lie Gabrielsen
Bioklynge Nord	Zølvi Pedersen
Biotec Pharmacon ASA	Dag-Rune Gjellesvik
Innovation Norway	Ole Jørgen Marvik
TTO Nord AS	Magnus Seppola

Organizers:

The MABIT program, NorInnova AS, TTO Nord AS and Bioklynge nord

Welcome to BIOPROSP 2006!

This is the Third International Conference on Marine Bioprospecting in Sub-Arctic Oceans. BIOPROSP 2006 will look at four major themes – Overall Resources and their Mapping, Bioactive Compounds, From Molecule to Market, and Commercialization Challenges and Strategies. During two packed days, we hope that you will be able to get a unique insight into the current situation trough presentations from leading Norwegian and international experts. We hope that the objectives of the symposium and your own expectations will be fulfilled, and are we looking forward to an interesting meeting and an enjoyable stay for all the participants!

The organizers

Contributors

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Program BIOPROSP 2006 Conference

Wednesday October 11th, 2006

National and international trends in Life Science: Research and Development

OPENING

8.30 – 9.00 **Registration**

9.00 – 9.10 **Opening of BIOPROSP 2006**
Jarle Aarbakke, President, University of Tromsø, Norway

MARINE RESOURCES

Chair: *Kjersti Lie Gabrielsen, Marbank, University of Tromsø, Norway*

9.10 – 9.40 **Marine resources of the north**
Ole Jørgen Lønne, Institute of Marine Science, Norway

9.40 – 10.10 **Repositories, sampling, logistics and screening**
David Newman, National Cancer Institute, USA

10.10 – 10.30 **The genome of *Vibrio salmonicida*; a good source for bioprospecting?**
Nils Peder Willasen, University of Tromsø, Norway

10.30 – 10.50 Coffee

BIOACTIVE COMPOUNDS

Chair: *Erling Sandsdalen, Fiskeriforskning, Norway*

10.50 – 11.20 **Marine bioactivities and drug discovery**
Marcel Jaspars, University of Aberdeen, Scotland

11.20 – 11.40 **Anti-microbial compounds from marine organism**
Tor Haug, Norwegian College of Fishery Science, Norway

11.40 – 12.00 **A new way of fighting bacteria**
Inge W. Nilsen, Norwegian Institute of Fisheries and Aquaculture Research, Norway

12.00 – 13.00 Lunch

Chair: *Jeanette Andersen, Marbio, University of Tromsø, Norway*

13.00 – 13.30 **Anti-tumour molecules and mechanisms; promising drugs**
Simon Munt, PharmaMar, Spain

13.30 – 13.50 **Cold adapted molecules exemplified with marine enzymes**
Arne Smalås, University of Tromsø, Norway

13.50 – 14.10 **Anti-tumour compounds and mechanisms from marine sources**
Stein Ove Døskeland, University of Bergen, Norway

14.10 – 15.10 Coffee and Poster session

Chair: *Guri Eggset, Hedmark University College, Norway*

15.10 – 15.30 **Search for inhibitors of the HIV-protease**
Helena Danielson, Uppsala University, Sweden

15.30 – 15.50 **Bioactivities in marine lipids; what are they good for?**
Bjarne Østerud, University of Tromsø, Norway

15.50 – 16.10 **Bioprospecting in the Trondheim Fjord**
Geir Klinkenberg, SINTEF Materials and Chemistry, Trondheim, Norway

19.30 Conference banquet dinner at Driv

Program BIOPROSP 2006 Conference

Thursday October 12th, 2006

Innovation

FROM MOLECULE TO MARKET

Chair: *Trond Ø. Jørgensen, University of Tromsø, Norway*

9.30 – 9.50 **The MabCent initiative in Tromsø**
Trond Ø. Jørgensen, University of Tromsø, Norway

9.50 – 10.10 **From molecule to market**
Svein Dahl, University of Tromsø, Norway

10.10 – 10.30 Coffee

10.30 – 11.00 **The scientist's dilemma; dealing with industry**
Alan Harvey, University of Strathclyde, Scotland

11.00 – 11.30 **The industrial challenge, dealing with scientists**
Simon Hinkley, IRL-BioPharm, New Zealand

11.30 – 11.50 **Marine enzymes, examples of commercial products**
Dag-Rune Gjellesvik, Biotec Pharmacon, Norway

11.50 – 12.50 Lunch

COMMERCIALISATION AND BUSINESS STRATEGIES

Chair: *Karl-Johan Jakola, NorInnova AS, Norway*

12.50 – 13.10 **Biobusiness, how to deal with ups and downs?**
Geir Gokstad, 4bio, Norway

13.10 – 13.40 **IPR strategies; "goodies" and "badies"**
Rebecca Gardner, Frank B. Dehn & Co, England

13.40 – 14.00 Coffee

PANEL DEBATE

14.00 – 14.20 **Marine bioprospecting; Visions for Norway?**
Ole Jørgen Marvik, Innovation Norway

14.20 – 15.30 **Panel debate – What is needed to bring Norway among the world's top nations in marine bioprospecting?**

15.30 **Adjourn**

Speakers BIOPROSP 2006 Conference

Jarle Aarbakke

Jarle Aarbakke has been Professor of Pharmacology and Clinical Pharmacology at the University of Tromsø since 1982.
His main research has been within cancer pharmacology related to genetic causes of interindividual differences in drug response. He has served as President of the University of Tromsø since 2002, and is now in his second 4 year term.

Ole Jørgen Lønne
Institute of Marine Science, Norway
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Ole Jørgen Lønne is at present heading Mareano. Mareano is an integrated mapping programme for the Norwegian seas and coastal areas carried out by the Institute of Marine Research (IMR), the Geological Survey of Norway (NGU) and the Norwegian Hydrographic Service (SKSK). The programme initiates a detailed mapping of the physical, chemical, biological environment of the sea-bottom areas of the southern Barents Sea in 2006.

Research areas: Ecosystem ecology. Polar marine ecosystems. Sea-ice associated communities. Benthic communities.

Education: Cand mag, University of Oslo, 1978. Cand real, Marine Zoology, University of Oslo, 1984. Dr scient, Marine Zoology, Norwegian College of Fishery Science, University of Tromsø, 1992.

Marine resources of the north

Abstract
Norwegian Sea areas out to 200 nautical miles from the coast cover an area of more than 2 million (2 057 826) km^2. A large part is in the north. The northern marine areas includes a variety of habitats ranging from sheltered coastal environments on the Norwegian mainland, the shelf areas of the Barents Sea, the deep areas of the Norwegian Sea to the seasonally ice covered areas around the Svalbard archipelago and the Arctic Ocean further to the north.

Among the living marine resources harvested in Norwegian waters are fish, crustaceans, scallops, seals and whales the most important. The institute of Marine Research is responsible for giving advice to national authorities on the status of the commercially exploited stocks. Quantitative advice is given annually on about 40 different species and another 40 species are followed closely.

Other resources are less well documented. In the Barents Sea alone there are more than 3000 different species associated with the seafloor. Both Russian and Norwegian scientists have conducted systematic surveys to document the diversity and productivity associated with the benthic habitat, but much information is still needed before we have the same understanding of the structure and function of the benthic communities as we do on other communities associated with the watercolumn.

The national mapping programme MAREANO was launched in order to improve our understanding of the role the benthos plays within the Barents Sea ecosystem. A detailed mapping of the physical, chemical and biological environment of the sea-bottom areas of the southern Barents Sea started in 2006.

In this talk I will give some examples of the potential marine resources associated with the northern areas with a special focus on organisms associated with the seafloor.

David J. Newman
Natural Products Branch, NCI, USA

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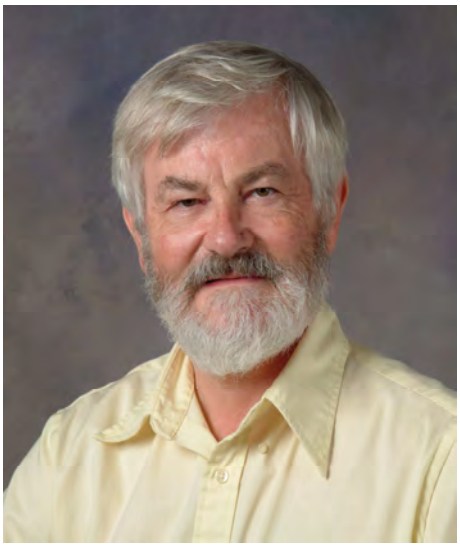

David Newman was born in Grays, Essex, UK. Initially trained as a chemical analyst he received a M.Sc. in Organic Chemistry (Liverpool) and then after time in the UK chemical industry, a D. Phil. in Microbial Chemistry from Sussex in 1968. Following postdoctoral studies at the University of Georgia, USA, he worked for SK&F (now GSK) in Philadelphia, PA, as a biological chemist predominately in the area of antibiotic discovery. Whilst at SK&F, he obtained an MS in Information Sciences in 1977 from Drexel University and following the discontinuance of antibiotic discovery programs at SKF, he worked for a number of US companies in natural products-based discovery programs in anti-infective and cancer treatments, joining the Natural Products Branch of the NCI in 1991, where he is currently Acting Chief and is responsible for the collection programs, the Open and Active Repository programs and provision of natural product-sourced chemical leads.

His scientific interests are in the discovery and history of novel marine and microbial natural products as drug leads in the anti-infective and cancer areas, in novel delivery methods for such agents and in the application of information technologies to drug discovery. In conjunction with Gordon Cragg (now retired), he has established collaborations between the NCI and organizations in many countries promoting drug discovery from their natural resources. He has published over 100 papers, presented over 60 abstracts, holds 17 patents that are related to these interests, is an UK Chartered Chemist and an UK Chartered Biologist and an EU Chartered Scientist and is also an adjunct full professor at the Center of Marine Biotechnology, University of Maryland.

Repositories, sampling, logistics and screening

Abstract
For any collection programme whose emphasis is on drug discovery and development in order to be successful, one has to be able to curate not only the organism(s) for taxonomic purposes, but also the samples and most importantly, the data as to where samples were collected and under what conditions.

In addition, one also has to be able to retrieve this information and then couple it to biological and chemical datasets from a multiplicity of sources. The presentation will describe how these tasks were approached at the NCI, where we found problems and how we have overcome most of them, and make recommendations as to methods to be considered for other groups as a result of our experiences.

Nils Peder Willasen
Institute of Medical Biology, University of Tromsø, Norway

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Research experience:
The fields of enzymology, protein production, structure-function studies, molecular modeling, genomics (comparative, functional and structural) and bioinformatics.

Academic degree:
PhD.(Dr. scient) in Biochemistry, University of Tromsø, 1992
Master of Science (Cand Real) in Biochemistry, University of Tromsø, 1992

Professional career:

Prof. of Biotechnology, University of Tromsø, 2002
Visiting scientist, EMBL, Heidelberg, 1999-2000
Assoc. prof. of Biotechnology, University of Tromsø, 1993
Research fellow, University of Tromsø, 1992-1993

The genome of *Vibrio salmonicida*; a good source for bioprospecting?

Abstract
Vibrio salmonicida is a psychrophilic ("cold loving") and moderate halophilic ("salt loving") fish pathogen belonging to the *V. fischeri* branch of the Vibrionaceae order. *V. salmonicida* is the causative agent of cold-water vibriosis (also called Hitra disease), of which outbreaks were predominant in wintertime at low water temperatures (<10^{o}C). The molecular mechanisms of host invasion, species specificity, colonization, growth and virulence properties are still largely unknown which makes *V.salmonicida* an interesting model organism for the study of primary as well as secondary adaptation (to temperature, salinity).

The complete genome has now been sequenced and annotated and for the first time a glimpse of a fish pathogen genome is available. Information from the genome sequence enables not only exploration of single biomolecules, pathways and networks, but also whole systems. A brief overview of how one can utilise *V. salmonicida* and the genomic information to provide molecules with new features and as a tool for the exploration of lead molecules (identification of target and mode of action), will be presented.

Marcel Jaspars
University of Aberdeen, Scotland

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Professor Marcel Jaspars is professor of organic chemistry at the University of Aberdeen. Research in the Jaspars group focuses on the functions and applications of natural products, particularly those from marine invertebrates. The goal of the work is to determine the biological role of selected natural products as well as using others as pharmaceuticals, tools for biomedical research, fluorosensors and catalysts.

Prof Jaspars was educated at Cambridge, where he enjoyed being supervised by Dudley Williams and obtained his PhD from Trinity College Dublin, Eire under the supervision of Tony Davis on organosilicon chemistry. A postdoc in Texas was swiftly followed by a longer postdoctoral stint in California with Phil Crews working on marine natural products. During this period he co-authored a textbook entitled 'Organic Structure Analysis'. Marcel Jaspars joined the faculty at Aberdeen in 1995 and was promoted to full professor in 2003. He was awarded the 2003 Matt Suffness award by the American Society of Pharmacognosy and has recently received a Research Development Fellowship from the UK's Biotechnology and Biological Sciences Research Council.

Marine bioactivities and drug discovery – Inhibitors of NF-□B from Fijian marine invertebrates

Abstract

Nuclear factor □B (NF-kB) is a family of transcription factors involved in a wide variety of diseases, including cancer and inflammation, and it has hence become a major target for drug discovery. Despite the abundance of marine natural products reported to have pharmaceutical activity, very little research has been performed to date on NF-kB inhibitory activity of marine natural products.

NF-□B is an inducible transcription factor found in virtually all cell-types. In the cytoplasm, NF-□B remains inactive as it is associated with the NF-kB inhibitory molecule I□B. Activated NF-□B is involved in the transcription of numerous genes involved in cancer, AIDS, Alzheimer's disease, arthritis, atherosclerosis, and inflammation in general. Due to its role in a wide variety of diseases, NF-□B has become one of the major targets for drug discovery. In particular, NF-kB is an ideal target for anticancer drug development for several reasons: NF-□B regulates the transcription of many genes involved in tumour promotion, angiogenesis, metastastis, and inhibition of apoptosis. Activated NF-□B increases resistance of tumours to chemo-and radio-therapy. NF-□B is constitutively activated by most types of tumours.

Numerous marine natural products have been reported with bioactivity in fields of cancer and inflammation, which are NF-□B-dependent pathologies, and one can expect to find out that the bioactivity of some of these compounds is actually due to their interference with the NF-□B activation pathway. This presentation will describe a screening programme carried out to identify marine natural products with potent NF-□B-inhibitory activity. In several cases, the mechanism of action was also elucidated in detail.

A total of 224 crude extracts from Fijian marine organisms, including algae, seasquirts, soft corals, echnoderms, and sponges were screened using a luciferase reporter gene assay. Out of these roughly 9% showed strong NF-□B inhibitory activity. A number of these extracts were selected to identify the chemical constituents responsible for this activity. Organisms chosen further study were the sponge *Rhabdastrella globostellata,* the soft corals *Sinularia* sp *and Lobophytum* sp*,* and the *Crinoid Comanthus sp.* In all cases the compounds responsible were isolated, structurally characterised and details of their mechanism of action were determined.

Tor Haug
Norwegian College of Fishery Science, Tromsø, Norway

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Present position: Associate Professor.

Education:
Biologist (*Candidatus scientiarum*),1994.
Authorised Aquamedicine Biologist, 2002
Doctor scientiarum in biology, 2004.

Teaching:
Pharmacology and Marine Biotechnology

Research area:
Marine bioprospecting/drug discovery – with focus on antimicrobial molecules.

Antimicrobial compounds from marine organisms

(**Tor Haug**, Klara Stensvåg, Sigmund Sperstad, Chun Li, Olga Soleng, Victoria Paulsen & Olaf B. Styrvold.)

Abstract

Marine organisms are a rich source for discovering novel bioactive compounds with therapeutic potential. Our aim (*the bioprospecting group* at the Dept. of Marine Biotechnology) is to isolate and characterise novel antimicrobial molecules from marine organisms collected from the Arctic or/and sub-Actic region. Here, we report our recent findings on antimicrobial peptides (AMP) in marine crustaceans, echinoderms and fish. In eukaryotes, AMPs form the first line of host defence against pathogenic infections and they are considered as key components of the innate immune system in invertebrates and vertebrates.

Due to their potent and often rapid lytic activity against microbes, and their mechanism(s) of action (dissimilar to conventional antibiotics), AMPs have emerged as promising candidates for a new class of antibiotics. Using bioassay-guided purification, several AMPs were isolated from the blood cells of the small spider crab, *Hyas araneus,* and the green sea urchin, *Strongylocentrotus droebachiensis*. The peptides belong to different antimicrobial peptide families based on their primary structures. Some of the peptides contain modified amino acid residues, which may protect the peptides from enzymatic degradation. An AMP isolated from Atlantic wolffish (*Anarhichas lupus*) skin was identified as an antifreeze-protein, indicating that AMPs may have several biological properties.

Inge W. Nilsen
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Nilsen entered his professional career by studies of DNA damage and repair in the research group lead by Hans Krokan at the Biochemistry Department, University of Tromsø. 4 years later followed a one year engagement at the Department of Medical Genetics (University Hospital) before returning to the University and joining the Biotechnology Department for 6 years.

After a short stay in Stuart Levy's lab, Tufts University (Boston, USA) working on antibiotic resistance, Nilsen started his work on Fiskeriforskning in 1996. Here his main interest of research has been on the discovery and application of enzymes and genes from marine organisms. This includes cold-adapted DNA-modifying enzymes and enzymes involved in detoxifying and in host defence (i.e. lysozymes). Currently, the main focus in his work is related to lysozyme inhibitors and inhibitors of viral proteases.

A new way of fighting bacteria?

Abstract
Bacteria have evolved many strategies for defence against antibacterial weapons in their surroundings as well as in potential hosts for infection. The innate immune system is an important first-line response for any infected host and constitutes various components such as antibacterial peptides, proteases and protease inhibitors as well as lysozymes.
Only recently it was discovered that bacteria, mainly Gram negatives, produce specific lysozyme inhibitors that have high capacity to bind to and thereby block the action of some lysozymes. On-going work has revealed several novel lysozyme inhibitors demonstrating a wide distribution among bacteria.

Furthermore, our work has shown that particular lysozymes that are not affected by these inhibitors display broad-range antibacterial activities on bacteria that produce inhibitors for other types of lysozymes.
Taken together, these findings have encouraged us to aim for a certain type of molecules that can suppress the lysozyme inhibitors and, thus, enable any type of lysozyme to promote lysis of most bacteria otherwise not susceptible to lysozyme-mediated killing.

Simon Munt
PharmaMar, Spain

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Simon Munt has over fifteen years experience within the pharmaceutical and biotechnology sectors and a broad experience of discovery and development, new product introduction, technology transfer and project management activities within the industry.

He currently works for PharmaMar in Madrid (Spain) as Medicinal Chemistry Manager within R&D, with responsibility for chemistry, analytical and pharmaceutical development activities.

Simon previously worked as a Project and Team Manager for GlaxoWellcome (now GSK) in the UK and Singapore, and was involved in technology transfer and late-stage development projects within Worldwide Manufacturing & Supply. Simon holds a First Class Honours Degree in Chemistry from the University of Durham and a Doctorate in Organic Synthesis from the University of Oxford.

From Bioprospection to Bioactive Molecules in Oncology

Abstract
PharmaMar is a Spanish biopharmaceutical company dedicated to **advancing cancer care through the discovery and development of innovative marine-derived medicines**.
The natural evolution of marine life forms over many millions of years has created great biological and chemical diversity that remains largely unexplored.

PharmaMar has recognized the richness of this chemical diversity and is actively involved in the discovery and development of **marine-derived bioactive compounds** as innovative treatments for cancer.

After almost two decades of bioprospection and research, PharmaMar has built up a **unique collection of marine invertebrates and microorganisms** and has discovered **many new families of bioactive compounds** with novel chemical structures.

Such novel chemical structures often result in **new modes of action** against tumour cells, thereby further enhancing the potential utility of such marine-derived compounds as therapeutic agents.

PharmaMar has **six compounds in clinical development** and an **exciting drug discovery and development pipeline**. More than 4,500 cancer patients have been treated with PharmaMar agents in clinical trials in Europe, US and Canada.
The presentation will demonstrate how PharmaMar has successfully used **Bioprospection** to discover and development Innovative **BioActive Compounds** to enhance Cancer care.

Arne Smålås
Department of Chemistry, University of Tromsø, Norway

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Arne O. Smalås is professor in physical chemistry and structural biology at the Department of chemistry, University of Tromsø. He is now the director of the Norwegian Structural Biology Centre (NorStruct). He has an additional affiliation as adjunct professor (professor II) in structural biology at the Department of biotechnology, Norwegian University of Science and Technology, Trondheim.

His research interests are within structural biology with X-ray crystallography, molecular modeling and biophysical methods as main research tools. He is involved in projects connected to cold adaptation of proteins, protein-protein recognition and interactions, and structural genomics studies on the psychrophilic and fish pathogenic bacterium, *V. salmonicida*.

Cold adapted molecules exemplified with marine enzymes

Abstract
The unique features of cold adapted enzymes have for several decades been exploited in industrial processes and more recently in various molecular biology applications. However, the potential is probably much higher, in particular for more specialized applications. In addition to the search for new enzymes with unique features, we have focused on structure-function relation studies of the cold active enzymes. A thorough insight into the molecular and structural basis for the unique features will allow for more sophisticated applications, and further on for redesign to optimize or alter certain properties by the use of protein engineering.

Comparative studies with enzymes expressed by organisms adapted to higher temperatures have, in combination with mutational analysis, frequently been used to obtain detailed information about the structural basis for cold activity. The structure-function relationships are in most cases complex, and are additionally complicated by the fact that most proteins (in particular the extra cellular ones) are in parallel subjected to other adaptive forces. For extra cellular proteins from cold adapted marine organisms for example, the high salt concentration must be taken into account when deducing the molecular basis for cold activity. This will be exemplified by the Endonuclease I from cold and warm adapted Vibrios.

Stein Ove Døskeland
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MD, Univ. of Bergen 1973 (10.53)
PhD, Univ. of Bergen (1981)

Current positions:
Prof. I Dept. Biomedicine, Med. faculty Univ. of Bergen. (Leader Cell Biology Research Group at Med. faculty since 1981).
Prof. II (proteomics) at Univ. of Tromsø.

Training abroad:
("visiting scientist"): 1982 -1983 (12 months): Howard Hughes Medical Institute (Prof. J. Corbin), Vanderbilt Univ. School of Medicine, Nashville, USA.
1989 (2 months): Dept. Pharmacology (Prof. G.S. McKnight), Univ. of Washington, Seattle, USA.
1992-1993 (12 months): IRIHN (Prof. J. Dumont), Med. Faculty, Univ.Libre Bruxelles., Brussels, Belgium.

Previous Researh Supervision:
For Doctoral Dissertations:
D. Øgreid (Dr.med. 1983), R. Ekanger (Dr. Med. 1989), O. Vintermyr (Dr. Med. 1990), A. Døskeland (Dr.Philos. 1991; supervision shared with T. Flatmark), G. Houge (Dr.Med. 1993), B.T. Gjertsen (Dr. Med. 1995), R. Bøe (Dr. Philos., 1995), G. Mellgren (Dr. Med. 1996), K. Fladmark (Dr. Scient. 1998), O.T. Brustugun (Dr. Med.1999), R. Hovland (Dr. Scient., 1999), T. Sandal (Dr. Philos., 2003), A. Christensen (Dr. Med., 2003), C. Krakstad (Dr. Scient., 2005), R. Kopperud (Dr. Scient. 2005), L. Herfindal (Dr. Scient., 2006).
For Master degrees:
R. Bøe (1989), K. Fladmark (1990), N. Aarskog (1992), T. Bruland

Marine micro-organisms - An unexpectedly rich source of agents able to kill cancer cells and modulate thrombosis.

Abstract
Most agents active against tumor cells act by inducing apoptotic cell death.
We have screened aquatic micro-organisms from a number of freshwater lakes, from brackish waters (The Baltic sea), and from coastal seawater (Portugal, Norway). Our conclusion is that bottom-dwelling microorganisms, especially from the sea, have most apoptosis-inducing activity. Several of them also produce anti-thrombotic substances. Examples of substances isolated from marine microorganisms and able to induce leukemia cell apoptosis and platelet inhibition will be given.

Helena Danielson
Department of Biochemistry and Organic chemistry, Uppsala University, Sweden

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Academic degrees
Prof. of Biochemistry, Uppsala Universitet, 2002-03-01
Assoc. Prof. of Biochemistry (Docent), Uppsala University, 1995-05-29
Ph. D. in Biochemistry (Filosofie doktor), Stockholm University, 1987-09-29
Thesis title: Structure-activity relationships in the catalytic function of cytosolic glutathione transferases.

Master of Science in Biochemistry, University of Rochester, Rochester, NY, USA, 1984-02-03
Master of Science in Chemical Engineering (Civilingenjör i kemiteknik), Lunds Tekniska Högskola, 1982-04-21

Academic position
Senior lecturer (Lektor), Dept. of Biochemistry, Uppsala University, 1994-07-01 -

Pre- and post-doctoral research experiences
Graduate student, Dept. of Biochemistry, University of Rochester, Rochester, NY, USA, 1982-83
Researcher, Dept. of Virology, Karolinska Institute, Stockholm, 1987-10-01 - 1988-06-30

Search for inhibitors of HIV-protease – the beginning of a new era in enzyme-based drug discovery

Abstract
Enzymes are important drug targets and enzyme inhibitors are effective drugs for a variety of diseases. Efficient and informative assays for identifying and characterizing enzyme inhibitors are essential in the early stages of drug discovery. We have combined conventional enzyme activity based inhibition assays with biosensor-based interaction assays in the search for inhibitors from different types of compound libraries, including natural product extracts.

These studies originated with the search for inhibitors of HIV-1 protease, and have evolved to include studies of a variety of enzymes including other proteases involved in viral diseases, fungal diseases and endogenous diseases, as well as polymerases from viral sources. Screening of compound libraries can be performed with both types of assays, while important issues of selectivity and resistance have been addressed with the sensitive biosensor-based assay, and confirmation of inhibitory effect is performed with an activity-based assay. The presentation will give an overview of the methods, strategies and types of results that can be achieved.

Bjarne Østerud
Institute of Medical Biology, University of Tromsø. Norway

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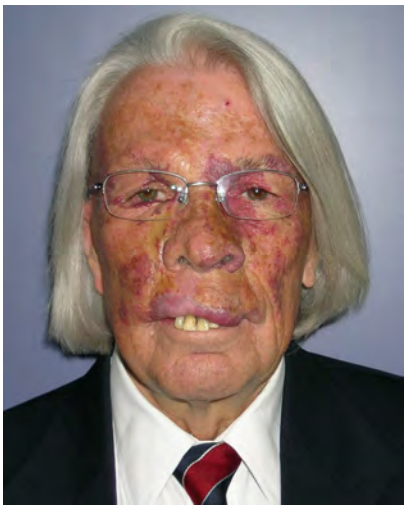

Major research interest:
Mechanisms of blood coagulation, infectious disease, sports medicine, atherosclerosis, effects of marine products on inflammatory reactions involved in coronary heart disease, thrombosis etc.

Østerud has published more than 180 articles in international journals and chapters in books.

Bioactivities in marine lipids, what are they good for?

(Bjarne Østerud and Edel O. Elvevoll)

Abstract
Seafood consumption is now well documented to be beneficial in prevention of many lifestyle diseases. The supplementation of diet with the marine n-3 fatty acids has been suggested to substitute beneficial effects of fish diet. Aspects like the impact of processing and preparation or presence and significance of additional beneficial substances in marine diets have not attracted the same attention and are still not fully explored.
What is the mechanism of marine lipid in prevention of CHD, thrombosis, psoriasis, asthma and several other western lifestyle diseases? One common denominator is anti-inflammatory effects.

Marine long chained polyunsaturated fatty acids, as EPA and DHA, exert their effects through enhancement of membrane fluidity whereby less phospholipase A2 (PLA2) becomes activated and subsequent reduction in release of arachidonic acid (AA, 20:4,n-6). This is one mechanism whereby the production of prostaglandins and leukotrienes are inhibited. The other way n-3 fatty acids down-regulate active prostaglandin and leukotriene products is mediated by the substitution of AA in the triacylglyecerols with EPA and DHA. The metabolized products of EPA and DHA, have only a minor pro-inflammatory effect compared to the products derived from AA.

The reduction in the prostaglandins and leukotrienes is associated with a significant reduction in the production of cytokines and oxidative products known to play an essential role in atherosclerosis and several other life style diseases where inflammation is the progenitor. However, it should be emphasized that excess of n-3 fatty acids in the absence of antioxidants may have adverse effects as the PUFA's are highly susceptible for rapid oxidation and cause aggravation in diseases associated with inflammation.
The suggestion of a possible association between seafood consumption and reduced cardiovascular risk, through the beneficial effects of additional, to n-3 fatty, beneficial components has been put forward and will be discussed.

Trond Ø. Jørgensen
Norwegian College of Fishery Science, Tromsø, Norway

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Professor Trond Ø. Jørgensen has published ca 85 papers in peer-reviewed journals within basic (tumour immunology) and comparative (fish) immunology, genetics, vaccinology, fish diseases and pathogens. He has coordinated 28 different research projects (2-4 years each), mainly funded by the Norwegian Research Council or industry.

Jørgensen has lectured in academic courses in basic and comparative immunology, fish diseases and genetics, and has supervised 26 Master and PhD fellows. He has been member of or led 35 different executive boards, boards of the Norwegian Research Council or programmes, various national and international committees, scientific advisory boards etc.

He is the present scientific manager of the Marbank and Marbio platforms (see above). Since 1998, the executive leader of the MABIT programme, an initiative on applied marine biotechnology research, funded by the Norwegian Department of Fisheries in addition to marine biotech industry. He is also the present deputy dean of the Norwegian College of Fishery Science, University of Tromsø.

The MabCent initiative in Tromsø

Abstract
The Norwegian Research Council, The University of Tromsø and six industrial and research partners have decided to collaborate in a consortium (MabCent-SFI), exploring the marine resources of the north.

As a marine environment, the high Arctic is unparalleled with respect to combination of temperature and light regimes. This implies evolution of a variety of organisms with unique physiological and biochemical adaptations and with correspondingly good prospects for finding novel lead compounds and bioactives. The MabCent-SFI integrates various disciplines and partnerships of academics at University of Tromsø (UoT) and expert SMEs, which covers the pipeline from biology of marine resources/species through screening and research on bioactives to commercialisation of drugs and biotechnological and nutraceutical products. The resources to be focused are marine bacteria harvested on the surface of the ice pack or frozen sediments, marine algae sampled under different blooming conditions and the huge variety of benthic invertebrates found in the Arctic seas.

The newly established National Marine Biobank in Tromsø, Marbank, will organise the sampling and produce extracts to the "medium-high-throughput" screening platform, Marbio. Compounds and molecules active against bacteria, tumour cells and inflammation as well as immunostimulants and various enzymes will further be isolated and characterised by their structure and "mode of action" at the NorStruct, SmallStruct and FUGE-N-facilities at UoT and by MabCent partners. All these technological platforms are state-of-the-art equipped for the tasks and targets planned in the MabCent operation. The four commercial MabCent partners will act in an R&D synergy although at different levels and arenas (pharmaceuticals, nutraceuticals, research tools etc.). Through their interaction with the interdisciplinary expertise at UoT and academic partners, the MabCent initiative will positively nurse research and innovation and setting standards for future marine-based discovery and development in Norway.

Svein G. Dahl
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Svein G. Dahl has been a Professor of Pharmacology at the Faculty of Medicine, University of Tromsø, Norway, since 1982. In addition to an academic career, he has worked 7 years in the pharmaceutical industry, including 3 years as the Director of Reseach at Jouveinal/Parke Davis, Paris (1994-1997).

He has conducted research in collaboration with several pharmaceutical companies, including Nycomed, Oslo and Synthelabo, Servier and Jouveinal in France. He is currently a member of the Board of Directors of Lytix Biopharma AS, a Norwegian pharmaceutical company dedicated to the discovery and development of novel treatments for drug-resistant infectious diseases and cancer (http://www.lytixbiopharma.com/).

From Molecule to Market

Abstract

The process of bringing a molecule to the pharmaceutical market starts with a drug discovery phase, followed by clinical studies. Drug discovery is usually initiated with exploratory research that may result in identification of a new molecule with desired biological activity. This is followed by a lead optimisation (”drug design”) phase, where chemical structure-activity relationships are studied and used to make compounds that are optimised regarding pharmacological effect, side effect profile and biopharmaceutical properties.

After a pre-development phase, where larger quantities of the compound are synthesised and more extensive preclinical studies carried out, the compound may enter the 3 phases of drug development: In Phase I the compound is administered to human volunteers in single, then repeated doses, in order to study tolerance and pharmacokinetics in man. In Phase II the compound is given to patients in a controlled, double-blind study of its efficacy after different doses. In Phase III the efficacy and side effect profile of the compound is studied in a larger number of patients, always in a controlled, double-blind fashion, usually compared to placebo and/or a comparator drug. The cost of discovery and development of a new drug is currently estimated to ~800 000 000 USD, and increasing. The time frame is 8 - 12 years or longer.

Why is it so expensive to discover and develop a new drug? Successful drug discovery relies on innovation and creativity, and the choice of molecular target is crucial. In clinical drug development, speed and cost/efficiency is essential. In spite of a rapid technical development in the post-genomic era, with combinatorial chemistry, advanced genomics, proteomics and high throughput screening methods, recent years have showed a slowdown, instead of the expected acceleration, in the number of new innovative medical therapies reaching patients. Only on average 11% of all compounds entering into Phase I studies make it to the market, and more than 70% of the costs are spent in drug development. Early attrition is therefore essential, such that termination of the development of a new compound occurs in the earlier phases. The average success rate in each phase of drug discovery and development implies that a successful drug candidate reaching the market is preceded by about 50 exploratory research projects and 20 different lead optimisation projects.

In order to discover and develop drugs today, it is therefore necessary to have

- Financial resources
- A clear business and R&D strategy
- Technical superiority
- - but also a bit of luck

A novel approach to identification of compounds with biological activity, as represented by marine bioprospecting in sub-Arctic oceans, may represent a competitive advantage in drug discovery. The choice of proper, disease-related molecular targets for development of such compounds will be essential for their chance of making it to the pharmaceutical marketplace.

Alan Harvey
Institute for Drug Research, University of Strathclyde, Glasgow, UK

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Alan Harvey has a background in neuropharmacology and current interests in the use of natural products for drug discovery. Since 1988, he has led the Strathclyde Institute for Drug Research, a collaborative centre in the University of Strathclyde in Glasgow that encourages interactions between academic researchers and industry.

SIDR has worked with 50 companies throughout the world and has attracted more than £20 million in industrial funding. SIDR has been used as the model for PharmaLinks, a joint initiative of the Universities of Strathclyde and Glasgow aimed at developing inter-university biomedical research collaboration and increasing the commercialisation of the two universities' pharmaceutically relevant research. Alan Harvey is Co-Director of PharmaLinks.

Alan Harvey is also involved in a wide variety of early-stage drug discovery projects from natural products. Along with colleagues from phytochemistry, he has assembled a highly diverse collection of plant extracts that is used in random screening; he coordinates the bioassay development and screening teams. This has led to several patent applications and numerous leads that are currently being followed up in different therapeutic areas.

The scientist's dilemma: dealing with industry

Abstract
This presentation will cover aspects of dealing with industry, stressing how to avoid the pitfalls and maximise the benefits.

Academics do have a dilemma, which relates to the sometimes conflicting needs of publishing the results of their research in scientific journals and of attracting further funding for the more commercially attractive aspects of their research activities. In approaching industry for financial support, academics have to realise that they have to work against several common preconceptions about dealing with academic institutions. They also have to be aware of how to place their work in the context of the competitive commercial landscape.

While many types of academic-industrial interactions are possible (e.g., sponsored research studentships, direct support of research, collaborations, consultancies, contract research, material transfer, technology transfer), it is important to define in advance what will be the best match for the requirements of the academic scientist, the academic institution and the funding company. Tensions and conflicts can arise, but these can often be avoided by fuller discussion and better communication within the academic institution before companies are approached.

When it comes to contract negotiations, there are various pitfalls to avoid, both internally and externally. Hopefully, by being aware of these possible difficulties, the chances of them arising can be minimised. Some case studies will be presented.

Simon Hinkley
IRL-BioPharm, Lower Hutt, New Zealand

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Simon Hinkley has a background in natural products chemistry (University of Otago, New Zealand) and post-doctoral work with Prof. Bruce Jarvis (University of Maryland at College Park, USA) led to taking up a position with IRL-BioPharm (Industrial Research Limited, New Zealand) in 1999. Specialist expertise focusing on;

- Management of production operations for the cGMP manufacture of active pharmaceutical ingredients (API's)

- High-potency chemical manipulations, specifically cytotoxins

- Microbial fermentation, purification and chemical modification

- Research and development in the area of natural product isolation, antibody-drug conjugates and process scale-up.

Marine biopharmaceutical manufacturing: a case study

Abstract
The first cGMP pharmaceutical produced in a high salt media using stainless steel fermenters will be discussed. An introduction to the technical issues faced in this type of manufacturing and solutions to specific issues will be discussed, in particular:

- Manufacturing of high potency fermentation derived secondary metabolites (specifically cytotoxins)
- Scale up for clinical trials of fermentation processes
- Fermentation in high-salt media

Company profile
IRL-BioPharm is a cGMP contract manufacturing company focusing on high-potency, small-molecule production from novel fermentation sources for early-stage clinical trial applications. Current areas of research are focused on novel cytotoxic chemicals and their chemical modification and utilization in antibody-drug conjugate therapies.

Dag-Rune Gjellesvik
Biotec Pharmacon ASA, Norway

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Dag Rune Gjellesvik, born in 1955, studied biochemistry at the University of Bergen, and in 1992 he received his Dr. Scient. degree in biochemistry. The subject for the Dr. thesis was enzymes in the lipid digestion system of fish.

After a short post doc period in Bergen, he moved to Tromsø and started to work in Biotec Pharmacon ASA (then Biotec Mackzymal) as product manager for marine biochemicals. Soon he entered the position of R&D Manager in the company, working with discovery and developement of both marine enzymes and yeast beta glucans.

Today he is responsible for the company's research activities within the area of marine biochemicals and marine bioprospecting.

Marine Enzymes – examples of commercial products

Abstract
Enzymes from organisms of the cold marine environment of the Arctic are adapted to low temperatures. That implicates that besides being more active at lower temperatures, they usually are less stable at higher temperatures. This provides an "off switch" that can be very useful when using these enzymes for analytical purposes.

Biotec Pharmacon ASA has for some years now produced and marketed marine enzymes for use as catalytic tools in genetic research and diagnostics. This presentation will show some examples of these applications, and how the heat lability comes in useful and provides extra convenience for the users.

PCR is a powerful method for amplification of specific DNA or RNA fragments. The method can copy DNA fragments hundreds of millons fold, and by that as few as 2 - 10 molecules of nucleic acid may be detectable. The high sensitivity of the method renders it very vulnerable for contamination, especially from previously made PCR products since these are in such high abundance in the lab. The problem may be reduced by rigorous procedures, but also enzymatic methods are available to eliminate the problem. However, these methods are not without drawbacks, but the presentation will show how two of Biotec Pharmacon's marine enzymes may alleviate these drawbacks by virtue of their heat lability and other properties.

Commercialisation andBusiness Strategies

Geir Gokstad
4bio AS, Oslo, Norway

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Geir Gogstad, Ph.D – senior executive with broad experience from key positions in Norwegian life science companies, including Nycomed, Genomar, Axis-Shield, and Genpoint, – and from seed capital financing (Start Foundation).

Responsible for development of highly successful diagnostic R&D products, including NycoCard, a best-selling product line of rapid immunoassays. Specialist in IPR strategies and execution of IPR. Previous board positions in Mison, Nycomed Pharma, Affitech, Oslo Research Park, as well as Functional Genomics (FUGE) and other programs of the Norwegian Research Council.

Actively involved in research and industry policy for many years. Educated in biochemistry from the University of Oslo, and holding a Dr.philos degree in biomedicine. Currently partner in the advisory company 4bio AS located in Oslo, Norwav.

Bio business, how to deal with ups and downs?

Abstract
The history of bio business is short, but even so it has been a turbulent event ranging from brilliant successes to the most humiliating fiascos. Since the early days of biochemistry, it was evident that this science could open for new dimensions in many disciplines. Not least the expectations from bio prospecting activities where predicted to have a bright future. But biotechnology has indeed earned its reputation as a risky, capital intensive, and time-demanding business area.

The typical “ups” related to bio business is in the optimistic start, the grant of patents, the moments of signing partnership contracts, and whenever a project is successfully resulting in sales of a product.
The first typical “down” is what happens between start and product launch, on the long and winding road called “product development”. Unforeseen technical obstacles, delays and moderately educated investors running out of patience, (and occasionally also out of money) are common elements in biotech business development.
Another “down” is related to financial market fluctuations when capital can be very expensive and often diluting the gründer(s) out of their owner position(s).
And what about patent rights? Are you infringing someone’s rights? You better have to analyse the situation thoroughly before you start. Please also keep in mind that the better your patents be, the more you shall be prepared to defend them.
Another challenge may show up after a successful product development. Never underestimate the demands of the distribution and sales process. There are many brilliant products that you probably never have heard about. Getting attention for your product in a world crowded with everyday information at all levels requires a dedicated partner that should be brought into the loop at an optimal stage.

Receipts for getting through are careful and educated project planning, strict focus on the critical part to reach the goals, honest and experienced communication to your investors, always consider how and when to join forces with other business operations, take capital whenever available rather than risking financial market drainage, and carefully consider adjustments in the crew to ensure that the management is optimal at all stages in the project. A good management is not necessarily good in all phases of business development.

Good luck!

Rebecca Gardner
Frank B. Dehn & Co, England

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After a degree in biochemistry Rebecca joined Frank B. Dehn & Co., one of Europe's leading firms of patent attorneys, in 1994. Qualifying as a British and European Patent Attorney, and now a partner, she works for a variety of UK and International clients in the life science field.

Rebecca has been working closely with Norwegian and other Scandinavian inventors and Intellectual Property owners for over 10 years. Her practice is focused on portfolio development, drafting and prosecuting patent applications through to grant and defending them where necessary. Working as the primary patent professional for companies and academic institutions has also seen her advising on enforcement of patents and the impact of third party patent rights.

She has had the opportunity to be involved with innovations in the pharmaceutical field as well as agroscience, human and animal nutrition, the oil industry and the area of scientific and laboratory tools. She has worked on patents for newly isolated genes and proteins, on techniques of nucleic acid isolation and characterisation, for therapeutically relevant peptides and stem cell technology, as well as cases relating to biologically active organic and inorganic compounds.

IPR Strategies; “goodies” and “badies”

Abstract
A presentation which highlights some of the key stages in the life-cycle of an invention: when and where to file a patent application, how much it costs to keep your patenting options open for twelve months and for two and a half years. When to nurture and when to be ruthless with members of your patent "family". Encouraging internal disclosure of innovation and external secrecy. Also looking at third party patent rights, your "freedom to patent" as opposed to your "freedom to operate" and how to minimise the costs of attacking someone else's patent.

Ole Jørgen Marvik
Innovation Norway, London

E-mail: o.j.marvik@4bio.no

Ole J. Marvik is the coordinator of Innovation Norway's life science sector activities as well as business advisor to their London office. Managing partner of the consultancy firm 4bio AS. Marvik is the founder and former CEO of Affitech AS, a drug discovery company based in Oslo and San Francisco.

He is also cofounder of the diagnostic company Genpoint AS and has been actively involved in Norwegian research and industry policy through several board positions (The Research Council, Oslo Research Park, Medcoast Scandinavia and Europabio), as well as being a co-founder and former chairman of the Norwegian Bioindustry Association). Marvik is PhD in biotechnology and holds a master's degree in management.

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Poster 1

Marine Phospholipids (MPL): The third generation of omega-3 products

Erik Løvaas
BioSea Management AS, Tromsø, Norway

Marine phospholipids (MPL) are valuable components that can be applied within diverse areas like nutrition, pharmacy, medicine as well as within basic research. MPL is characterized by having a high level of omega-3 fatty acids in the 2-position of the glycerol backbone. MPL can be extracted from diverse marine raw material, in particular from roe and krill but also from by-products from the fishery industry. The poster outlines the chemical characteristics of marine phospholipids, their natural resources and their applications. Amongst applications, 'brain feeding' will be emphasised, as deficiency of omega-3 fatty acids in the brain induce memory and learning impairment, as well as psychological disorders.

Poster 2

Pro-apoptotic and Anti-apoptotic Compounds Isolated from Baltic Sea Cyanobacteria

Lars Herfindala, Linn Oftedala, Jouni Jokelab, Matti Wahlstenb, Frode Selheimc, Perttu Permid, Camilla Krakstada, Rune Kleppea, Kaarina Sivonenb, Stein Ove Døskelanda

a Department of Biomedicine, Section for Anatomy and Cell Biology, University of Bergen
b Department of Applied Chemistry and Microbiology, Division of Microbiology, University of Helsinki
c Department of Biomedicine, Proteomic Unit (PROBE), University of Bergen
d Institute of Biotechnology, NMR Laboratory, University of Helsinki

In order to identify natural products from marine organisms, benthic marine cyanobacterial species were screened for content of bioactive compounds. Biomass from 43 cyanobacterial isolates were sequentially extracted with solvents of decreasing polarity. These crude extracts were screened for contents of natural products inducing apoptosis in a rat promyelogen leukemic cell line (IPC-81 wt). Of the 43 isolates tested 21 induced 50-100% apoptosis in the IPC-81 wt cells. The different extracts were also screened for content of bioactive compounds in primary rat hepatocytes and 14 isolates induced 50-100% apoptosis. Several types of death morphology were observed in the hepatocytes incubated with these crude extracts. Some extracts induced a death morphology similar to microcystin and nodularin, whereas others induced a distinct and novel death phenotype.
The apoptogenic compound M23, which induce apoptosis in both primary hepatocytes and promyelogenic leukemia cells, was purified from the cyanobacterial isolate number 23. Cell death induced by M23 was marginally dependent on caspase activation and could only minimally be inhibited by overexpression of the anti-apoptotic protein Bcl-2.

A novel bioactive peptide, M1, was able to completely protect primary rat hepatocytes against the apoptogenic hepatotoxins microcystin and nodularin by inhibiting their cellular entry. M1 did not protect against intracellularly delivered phosphatase inhibitors or against apoptogens acting via membrane receptors, like TNFalpha and TGFbeta. Moreover, M1 inhibited nodularin-associated protein phosphorylation, but did not interfere with intracellular microcystin-induced death-signalling events like CaMKII-dependent protein phosphorylation. M1 was tested against several mammalian cell lines at concentrations up to 0.1mM without showing any sign of toxicity and appears therefore to be a non-toxic inhibitor of microcystin-induced cell death.

Poster 3

ISOLATION OF A NOVEL ANTIMICROBIAL PEPTIDE FROM THE GREEN SEA URCHIN, Strongylocentrotus drobachiensis

Chun Li*, Tor Haug, Olaf B. Styrvold, Trond Ø. Jørgensen and Klara Stensvåg

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Antimicrobial peptides (AMPs) play an important role in the innate immune system in the defense against microorganisms. There have been many AMPs discovered from invertebrate animals. The sea urchin, a potential source for the discovery of new AMPs, possesses a non-adaptive, innate immune system. In our previous study, the antibacterial activities were detected in extracts of coelomocytes from the green sea urchin, Strongylocentrotus drobachiensis. Several peptides were isolated showing relatively high antibacterial activity against both Gram-positive and Gram-negative bacteria. One of the active peptides was purified by HPLC and characterised by mass spectrometry (MS) and Edman degradation sequencing.

In order to further identify this peptide, a cDNA library was constructed from the green sea urchin coelomocytes. The gene coding for the peptide was cloned and sequenced. The peptide is composed of 89 amino acids in total, where 38 amino acids represent a prepro sequence and 51 amino acids represent a mature peptide. The mature peptide contains six cysteine residues which is similar to the defensin class of AMPs. Furthermore, the mature peptide contains 11 positively charged amino acids which cause a positive charge of this peptide. This might explain the high antibacterial activity of this AMP.

Poster 4

HYASIN, A PROLINE-RICH ANTIMICROBIAL PEPTIDE FROM THE SMALL SPIDER CRAB, Hyas araneus.

Sigmund Sperstad*, Tor Haug, Olaf B. Styrvold, and Klara Stensvåg.

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Lacking an adaptive immune response, marine invertebrates rely on physical barriers and components of the innate immune system in their defence against pathogens. Among the reservoir of host-defence components, the natural antibiotics have been shown to play an important role in the immune system of invertebrates.

Several antimicrobial peptides (AMP) have been isolated and partially characterised from the haemocytes of the small spider crab, Hyas araneus. One of these, named hyasin, showed antibacterial effect against both Gram negative and Gram positive bacteria in µM concentrations. Through a cDNA library, the hya transcript has been cloned and sequenced. It coded for a pre-peptide of 45 residues, with a signal sequence of 23 amino acids and a mature, active peptide of 22 amino acids. Proline and arginine were the numerical dominant amino acids, arranged as six RP-repeats. The peptide showed no homology with already known members of the proline-rich group of AMP. Furthermore, the active peptide contained a post-transcriptional modified tyrosine-residue. Mass spectrometry data indicated that the tyrosine is di-bromated. A real-time RT-PCR approach showed that the gene mainly is expressed in the haemocytes, but expression was detected in all the tissues examined.

Studies to investigate the expression and immunolocalisation of the peptide are in progress.

Poster 5

Marbank – a repository for marine resources

Kjersti Lie Gabrielsen and Robert A. Johansen
Marbank, University of Tromsø, N9037-Tromsø, Norway

Marbank is a setup for collection and preservation of marine resources/organisms for scientific research, commercial opportunities and exploitation purposes. The main objective of Marbank is to provide an accessible national repository of frozen marine biological samples, collected and maintained under rigorously controlled conditions.

The material archived and stored in the Marbank repository includes taxonomic samples, gene material and biochemical extracts from marine microorganisms, plankton, algae, invertebrates and vertebrates. All information connected to the marine samples (field data, laboratory preparation etc.) is stored in a database.

Poster 6

MabCent – a Centre for Research-based Innovation of marine bioactives and drug discovery

Trond Ø. Jørgensen and Kjersti Lie Gabrielsen
MabCent, University of Tromsø, N9037-Tromsø, Norway

MabCent is a Centre for Research based Innovation hosted by the University of Tromsø. The paramount objective of MabCent is to find and develop high-value bioactive products through screening of Arctic organisms.

In addition to the interdisciplinary expertise at the University of Tromsø and academic partners, MabCent has four commercial companies as active partners acting in a consortium. The consortium covers the pipeline from biology of marine resources/species through screening and research on bioactives to commercialisation of drugs and biotechnological and nutraceutical products.

Multiple research vessels and the infrastructure platforms Marbank, Marbio, SmallStruct and FUGE-N represent important expertise, technology and instrumentation within the MabCent operation.

Poster 7

MARBIO – A platform for screening and exploration of unique bioactivities at the University of Tromsø

Espen Hansen*, Bernt Igeland, Trine Stiberg, Kirsti Helland and Jeanette Hammer Andersen.

*Marbio, Dept. Marine Biotechnology, Norwegian College of Fishery Sciences, University of Tromsø, N-9037 Tromsø, Norway

In 2005, Marbio was established at the University of Tromsø as a medium/high-throughput analytical platform with the aim of bioprospecting a large number of marine organisms from Arctic and sub-Arctic waters for potential drugs and/or lead compounds.

The platform has the capability to extract, purify and identify molecules within some of the most important drug areas. Up to now screening for anticancer, antibacterial and immunostimulatory molecules have been established. The methods used at Marbio for extraction, purification, dereplication and screening are outlined in this presentation.

Poster 8

The Norwegian Structural Biology Centre - NORSTRUCT

Department of Chemistry, Faculty of Science, University of Tromsø
Department of Molecular biotechnology, Faculty of Medicine, University of Tromsø
Department of Marine Biotechnology, Norwegian College of Fishery Science

NORSTRUCT is a national service and competence centre in structural biology, located at the Department of Chemistry, University of Tromsø. The Centre is established as a structural biology facility of international standard for structure determination and 3D analysis of biologically active macromolecules. NORSTRUCT is established through the Norwegian functional genomics initiative (FUGE) and it is financed by the FUGE-program and the University of Tromsø.
Activities are divided between local and external projects and the Centre seeks to streamline the processes starting from recombinant protein production to 3D structure determination using X-ray crystallographic techniques. Through participation in external projects, the Centre will offer the Norwegian molecular biology research community services, competence and instrumentation in a broad range of techniques in addition to serve as a link to international large-scale facilities such as the European Synchrotron Radiation Facilities (ESRF) in Grenoble.

Poster 9

"A step closer to the ultimate answer Structural studies of catalases from Vibrio salmonicida and Proteus mirabilis"

E.K.Riise*, M.S.Lorentzen, H.K.S.Leiros, R.Helland og N.P.Willassen

*The Norwegian Structural Biology Centre, University of Tromsø, Norway

Cold adapted enzymes have the properties to cope with the reduction of chemical reaction rates induced by low temperatures. Thermal compensation in these enzymes is reached, in most cases, through a high catalytic efficiency associated with a low thermal stability. Catalases catalyses the degradation of hydrogen peroxide, a reactive by-product of oxygen, to water and oxygen.
Previous studies have shown that the recombinant catalase from Vibrio salmonicida clearly possesses cold adapted features compared to the mesophilic homologue from Proteus mirabilis.

The aim of this study was to determine the 3D-structure of V. salmonicida catalase in order to obtain a greater understanding of the molecular basis for cold adaptation by comparison with and structural studies of P. mirabilis catalase.

Poster 10

Establishment and screening of an Arctic marine metagenome

Hans-Matti Blencke and Bjarne Landfald

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Microorganisms are precious sources of secondary metabolites and enzymes for biotechnological and medical use. However, the discovery of new bioactive substances by conventional screening methods has been hampered by the fact that the majority of microorganisms are not cultivable on synthetic growth media. This enormous pool of otherwise concealed biodiversity can be tapped by cloning the metagenome, i.e. isolating and cloning DNA directly from the environment, and subsequently screening it for bioactivity in cultivable host strains.

We are interested in the diversity and bioactive potential of Arctic marine habitats. Our work has so far focused on the intertidal zone, which is characterized by rather extreme environmental fluctuations and substantially higher bacterial densities than the adjacent seawater. Environmental DNA from a Svalbard intertidal zone has been isolated and cloned into large-insert fosmid vectors. (~30kb insert size) and a metagenomic library of about 30,000 clones in *Escherichia coli* EPI300has been established.

A screening for lipolytic activity with subsequent subcloning and sequencing of selected positive clones has been carried out successfully. We have, thereby demonstrated that the metagenomic approach is feasible for high-throughput screening of cold-adapted microbial enzyme activities.

Poster 11

Envision Software Package for the Concerted Study of Biological Data

Christopher G. Fenton

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Norway

Background

The study of proteins and protein families often require analysing and visualizing data from different sources; structures, phylogenies, alignments, etc. But problems quickly arise when trying to get the differing software applications to work together, or pose questions that cross data sources. The Envision software package attempts to solve some of these difficulties, by compiling the various file formats into an integrated queryable object repository, and providing standard viewer applications that share a common window event subsystem.

Results

Envision is an open source stand alone software package for the study of protein families. The package includes traditional graphical viewers for structure, alignment, phylogeny, plus additional viewers for information, data manipulation, and query interface. The Envision software package provides an integrated consistent graphical user interface with tutorials on how to enter, query and visualise data along with additional documentation. Biological data from several diverse sources; multiple sequence alignments, protein structures, phylogenies, etc, can be compiled into a central file based object registry.
Additionally, users can define properties. User defined colouring makes query results easy to visualize in viewers. Windows events like movement, selection, limits, query result, etc., can be shared among participating viewers to aid in direct comparisons. Multiple synchronized views of sequence alignments, structures, phylogenies, and worksheets and be synchronized aid greatly in contextual interpretation of biological data. Every effort has been made to keep Envision software platform independent. Work can be shared among scientist though a portable file based datasets and user generated executable scripts.

Conclusion

Envision software package is designed for molecular biologists that need to examine problems from several viewpoints, and need the views coordinated. Additionally, for molecular biologists that ask questions that span across traditional file format barriers, questions that span from phylogenic nodes to hydrogen bonds.

Poster 12

Identification of an 18 kDa Outer Membrane Protein in *Vibrio salmonicida* by Western Blot and Mass Spectrometry

Christian Karlsen, Steinar Paulsen, Sigrun Espelid and Nils Peder Willassen

Department of Molecular Biotechnology, Institute of Medical Biology, University of Tromsø, Norway

V. salmonicida, a marine environmental bacterium, is known to be the disease causing agent of cold water vibrosis in Atlantic salmon (*Salmo salar*), but little is known about virulence factors in *V. salmonicida*. This study identified and analysed an outer membrane protein (OMP) that is known to be immunoreactive (Espelid *et al*. 1988). OMPs from *V. salmonicida* were separated by SDS-PAGE. A protein, immunoreactive to monoclonal antibodies was localized by Western blot and successfully extracted from the gel. BLAST hits from the MS/MS analysis predicted the protein to be a peptidoglycan-associated lipoprotein (Pal), with a high homology to OmpA.

Poster 13

Prediction and validation of small non-coding RNAs (sRNAs) involved in iron homeostasis and quorum sensing in *Vibrio salmonicida* and *Vibrio fischeri*

Geir Hansen[1], Corinne Krentz[1], Rafi Ahmad[1], Peik Haugen[1], Steinar Paulsen[1,2], Nils-Peder Willassen[1,2]

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Bacteria such as *Vibrio salmonicida* and *Vibrio fischeri* respond to environmental changes by mounting coordinated genetic responses involving one or more regulators of expression. One example is the Ferric uptake regulator (Fur) involved in iron homeostasis. Fur regulates the expression of a known small, non-coding RNA (sRNA) named RyhB through a Fur binding site (Fur-box) in the promoter region of the *ryhB* gene. sRNAs can be found in all kingdoms of life where they carry out diverse functions, and many are regulators of gene expression. A biocomputational genomic search employing known transcription factors and genomic features, predicted potential sRNAs involved in iron homeostasis and quorum sensing in *V. salmonicida* and *V. fisheri*. The potential sRNA targets were amplified together with proteins thought to be involved in the two sRNA regulated systems to be used for ^{32}P radiolabelled probes in Northern analysis.

V. salmonicida and *V. fischeri* were grown under iron-limiting and oxidative stress conditions, and cells were collected from the cultures at the beginning, middle and end of the exponential growth phase. RNA molecules in the size range og 20 –1000 nt separated on 5% polyacrylamide/urea gels showed positive hybridization results for the sRNA homolog RyhB, one novel sRNA, sRNA2, and four mRNAs, Fur, Sod, AhpC and Catalase, thought to be involved in the iron regulatory system in both *V. salmonicida* and *V. fischeri*. For the quorum sensing pathways, the sRNA homolog Qrr was identified in both *V. salmonicida* and *V. fischeri*. Other predicted sRNAs (8, 11) were not found in *V. salmonicida* or *V. fischeri* under iron-limiting or oxidative stress conditions and further studies are needed to verify or disprove the predictions. Additional experiments have to be done to get a better understanding of the expression patterns and correlations between the different sRNAs and mRNAs.

Poster 14

Oxidative stress in *Vibrio salmonicida*

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Reactive oxygen species (ROS) can damage DNA, lipid membranes and proteins, and have been implicated in numerous diseases. ROSs form as a natural by-product of the normal metabolism of oxygen and have important roles in cell signalling. During times of environmental stress, ROS levels can increase dramatically. This can result in significant damage to cell structures and cumulate into a situation known as oxidative stress. Cells have evolved mechanisms to protect themselves against oxidative stress through enzymes such as catalase and superoxide dismutase, small proteins like thioredoxin and glutaredoxin, and molecules such as glutathione. Two major transcriptional regulators, OxyR and SoxRS, control bacterial responses to oxidative stress. Structural and functional studies are used to elucidate mechanisms involved in oxidative stress. The psychrophilic fish pathogen, *Vibrio salmonicida*, is used as a model organism.

Poster 15

Uracil-DNA *N*-glycosylase (UNG) from the marine psychrophilic bacterium *Vibrio salmonicida* shows cold adapted features

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Uracil-DNA *N*-Glycosylase (UNG) is a DNA-repair enzyme and is involved in the base excision repair pathway (BER) removing uracil from DNA.

Cold adapted enzymes are generally characterised by a higher catalytic efficiency, reduced temperature optimum and reduced thermal stability compared to their mesophilic counterparts. Increased flexibility and optimisation of electrostatic surface potential have been suggested as different strategies for adaptation to cold environments.

We have cloned, expressed, purified and characterised the recombinant UNG from the psychrophilic bacterium *Vibrio salmonicida* LFI1238 (vsUNG). The biochemical characteristics have been compared to a mesophilic counterpart, *Vibrio cholerae* UNG (vcUNG), to reveal possible cold adapted features of vsUNG. The crystal structure of vcUNG has been solved to 1.5 Å resolution. A homology model of vsUNG has been built based on the crystal structure of vcUNG.

Characterisation experiments demonstrated that both enzymes possessed the highest activities at pH from 7.0-7.5 and at salt concentrations in the range of 25-50 mM NaCl. Temperature optima for activity were determined to approximately 30ºC for vsUNG and 50ºC for vcUNG. Temperature stability of the enzymes was compared at 4ºC, 25ºC and 37ºC, and vsUNG was found to be more temperature labile than vcUNG at these temperatures. Kinetic studies at three different temperatures, 15ºC, 22ºC and 37ºC, demonstrated higher catalytic efficiency for vsUNG due to higher substrate affinity. The increased substrate affinity of vsUNG is probably caused by increased positive charges in the DNA-binding site of the enzyme. Thus, activity and stability measurements reveal typical cold adapted features of vsUNG. Two mutants of vcUNG (vcV90R and vcH194R) have been constructed and kinetic studies at 37ºC revealed higher substrate affinities, emphasizing the importance of these residues in substrate binding.

Poster 16

42 – answering the insolubility problem of *Vibrio* proteins expressed in *E. coli*

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To carry out structural studies proteins need to be overexpressed and purified in a soluble form. We encountered solubility problems trying to express proteins from the cold adapted species *Vibrio salmonicida* in *Escherichia coli* host cells. To improve the solubility of the proteins a screening system was set up where the effects of six different N-terminal fusion proteins and an N-terminal His_6-tag were compared. We chose seven different proteins: five from *V. salmonicida* and two from the closely related mesophile *Vibrio cholerae*.

Expression was tested in two different expression strains and three different temperatures (16℃, 23ºC and 37ºC), thereby producing 42 different conditions per gene. In general, we found great differences in the effects of the fusion protein on solubility and level of expression. His_6-tag was found to be the least efficient or among the least efficient tags, whereas MBP and NusA performed best. In most cases the level of expression increased with temperature whereas solubility decreased. We found no clear connection between the preferred expression temperature of the protein and the temperature of the organism's natural habitat.

Poster 17

"The *Vibrio salmonicida* genome project"

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The objective of the project is to investigate by innovative approaches the molecular nature of host-pathogen interactions between salmon (host) and *Vibrio salmonicida* (pathogen). Information from whole genome sequencing of *V. salmonicida* will provide us with the necessary tool to explore virulence and defence systems in the bacterium. The acquired knowledge will be essential in order to identify potential antigens and other proteins that may have application as vaccines, biochemicals or pharmaceutical drugs. Through functional (expression profiling and RNomics), structural (biochemical characterization and theoretical modelling) and comparative genomics, gene regulatory networks and metabolic pathways will be constructed *in silico*. By integrating biology and chemistry we will take a new and innovative approach to pathogenesis research.

Poster 18

Ferric uptake regulator: Its regulons and smallRNAs

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Background: Iron is required for all life forms, including bacteria. A wide range of biochemical reactions like oxygen transport, electron transfer and DNA synthesis are catalysed by iron. It is also important to control intracellular iron concentration. The biological function of iron is dependent upon its incorporation into proteins. In most bacterial species, this iron-dependent repression is mediated by a transcriptional repressor, ferric uptake regulator (Fur). Genes that are under the control of Fur form the Fur-regulon. When iron is abundant, Fur complex with Fe2+ and blocks transcription of target genes by binding to conserved promoter regions termed Fur-boxes. Fur is also known to regulate a small regulatory RNA called r*yhB,* which itself is shown to regulate around 40 genes in *V.cholera* and *E.coli*. Despite the information available on Fur-regulated genes in *E.coli* and other bacteria, there is still an underlying possibility that there are novel genes or systems that are unique to the vibrios. The identification could give new insights into understanding their virulence and pathogenesis. In this study, we apply the knowledge from known Fur-binding sites by building an alignment matrix to identify sites in five published vibrio genomes and in unpublished *V. Salmonicida* genome.

Results: The consensus Fur-binding site from our matrix is 5´AATGATAATNATTATCATT3´, which follows the both the 7-1-7 and the F-F-x-R arrangements as well as proposed 5'NATA/TAT3' hexamer unit shown to be necessary for high affinity Fur-DNA interactions. While many of the predictions made by this approach overlapped with the ones already identified by mircoarray analysis and binding assays, pointing to the accuracy of our method, a good number of novel Fur-regulated genes were additionally identified to be Fur-regulated. We also predicted a number of fur-regulated sRNAs using an in-house developed algorithm. Northern analysis was performed in
V. fischeri and *V. Salmonicida* to validate the predictions and we found the *ryhB* homolog and a novel sRNA (sRNA2). The Northern results also showed regulation of a number of novel-regulated genes.

Conclusions: Using a bioinformatics we identified a number of novel fur-regulated genes and sRNAs in sequenced vibrio genomes. Our analysis has revealed several novel Fur-repressed genes likely to be involved in iron-acquisition. Interestingly, two operons involved in energy metabolism were also predicted to be Fur-regulated. We also predicted Fur-regulation for a haemolysin gene (hlyA), chemotaxis and toxin co-regulated pilus systems that are probably involved in virulence. We hypothesise that Fur-regulates around 100 genes in all vibrio *spp*. Homologs of ryhB identified in *V. fischeri* and *V. salmonicida.* A novel sRNA of approx. ~ 60 nt (sRNA2) also identified in two vibrio species, probably regulated by Fur. Preliminary data suggest that sRNA regulation is a common feature in vibrios and many novel sRNAs are likely to be discovered in future.

Poster 19

Optimum Enzymatic Activity of Endonuclease I from Vibrio salmonicida and Vibrio cholerae Correlates With the Bacterial Growth Habitat

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Endonuclease I is a periplasmic or extracellular enzyme found in many Gram- bacteria. This enzyme from *V. salmonicida* (*Vs*EndA) and *V. cholerae* (*Vc*EndA) has been recombinantly expressed and purified. *V. salmonicida* is a marine, cold adapted bacterium, while *V. cholerae* is a brackish water, mesophilic bacterium. The periplasmic or extracellular localization of endonuclease I means that the enzyme is exposed to the outer environment of the cells. The optimum conditions, in terms of salinity, temperature and pH of the two enzymes, correlates well with the natural habitats where the corresponding bacteria lives. At physiological concentrations of NaCl the enzymes show only DNase activity as the RNase activity is inhibited by NaCl. The crystal structures of the two enzymes also reveal a totally buried chloride ion, which is normally only seen on the surfaces of proteins.

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