CENTRE FOR
MOLECULAR BIOLOGY
AND NEUROSCIENCE

ANNUAL REPORT 06

Centre for Molecular Biology and Neuroscience (CMBN)

Norwegian Centre of Excellence

UNIVERSITY OF OSLO

Rikshospitalet – Radiumhospitalet HF

SUMMARY

Looking back on 2006 – and on the way ahead

In December 2006 the Centre received the good news that it will be continued for another 5 year period – until end 2012. In fact, the Centre passed the half time evaluation with flying colors. The report recognizes the high productivity of the Centre and concludes "……*the Centre for Molecular Biology and Neuroscience is well organized and contributes importantly to provide better facilities for each of the eleven groups, which have complementary expertise in different molecular and neurobiological areas. All three evaluators ranked the research at the centre as* ***exceptionally good.***"

The positive outcome of the half time evaluation is a tribute to the devotion and enthusiasm of the entire staff associated with the Centre – and also attests to the strong administrative and financial support from the host institutions – the University of Oslo and Rikshospitalet-Radiumhospitalet Medical Centre. The half time evaluation report provides CMBN with a vote of confidence that will serve as an important backing for the Centre's activities and strategy towards 2012.

From CMBN I to CMBN II

The CMBN was designed to elucidate select biological processes (including genome instability, DNA damage and repair, glutamatergic transmission and ion transport, stem cells, brain development, and mechanisms of edema and infection) that are inextricably coupled to brain disease and the treatment thereof. The overriding aim was to build a knowledge base for new approaches to the treatment of brain disease and age-related neurological impairment. In its second period (CMBN-II), the Centre will retain its strong focus on basic research. However, it will concentrate its efforts on analysis of disease mechanisms and on pursuing new directions for therapy that have been revealed through discoveries and breakthroughs made in the Centre's first period (CMBN-I). Thus the Work Program for 2007 – 2012 includes *in vitro* approaches for drug design and testing, and analyses of patient cohorts, particularly in contexts where the Centre has provided a strong experimental base for such endeavours.

The continuation of the Centre will allow it to harvest the benefits of the major investments that were made in CMBN's first period. These investments have translated into the generation of new experimental models (including a wide range of transgene animals), the introduction of new technologies (including multiphoton *in vivo* imaging, animal-PET, proteomics, and structural biology), and the establishment of a number of national and international networks that broaden the expertise and intellectual capital of the Centre.

The new building -"interaction through key technologies"

The strategic preparation for CMBN-II coincided with the planning phase for the new building at Gaustad, close to Domus Medica. This building will be housing many technologies and infrastructure resources that are expected to stimulate biomedical research also outside of the Centre, and far beyond the life expectancy of the Centre itself.

Specifically, the new building is meant to provide a link between the basic scientists and the clinical research environments on the Gaustad campus and to serve as a resource and strategic asset for the region's biomedical research community at large. The technologies that will be established in the new building will bolster the competitive advantage of the research community, add to existing and new core facilities and help increase the success rate for applications to EU's seventh framework program and other international funding bodies. CMBN will play an active role in building up the facilities as a common resource that will outlast by far the life time of the Centre.

The functions and technologies that will be allocated to the new building include:

- High throughput tissue processing
- Proteomics/structure biology
- Imaging – including multiphoton imaging and PET/MR
- Neuro/bioinformatics
- Transgene technology/animal facilities
- Animal models (particularly in vivo models that will help facilitate translational research)

The Board of the University of Oslo decided in May 2006 that the building process should be initiated. It is essential that this process now proceed as planned and that we will see no further delays. Once the building is completed it will allow for an "interaction through key technologies" that will boost the output of the Centre and of other research groups that stand to benefit from the new facilities.

2006: Scientific output

The policy of the Centre is to publish its findings in leading peer-reviewed journals. Accordingly, a large fraction of the more than 60 papers that emanated from the Centre in 2006 appeared in journals with very high impact such as EMBO Journal, Nature Reviews Microbiology, Neuron, Proceedings of the National Academy of Sciences USA and FASEB Journal. Space does not allow for a description of the numerous discoveries and scientific advances that this long list of papers represents. Suffice to mention that the Centre has now reached most of the milestones that were embedded in the Work Program for CMBN I.

A main element in the Centre's publication strategy for 2006 was the preparation of a Special Issue entitled Genome Dynamics and DNA Repair in the CNS. Most of the papers scheduled to appear in this Issue were published in electronic version in 2006 (the hard copy version of the Issue will be published in spring 2007). Dr. Vilhelm Bohr, who is affiliated with CMBN as a Guest Professor, has played a central role in the compilation and editing of the Special Issue. His contribution is gratefully acknowledged.

The publication of the Special Issue is an important event in the life of the CMBN, not least because it directly addresses one of the concepts that motivated the establishment of the Centre: that knowledge of the mechanisms of DNA damage and repair could advance significantly our understanding of the mechanisms underlying neurodegenerative disease and brain ageing. In fact, the composition of the CMBN reflects our vision that a better understanding of brain diseases - and new approaches to the treatment of these - will arise by bringing together expertise in DNA repair with expertise in neurobiology. While the development of new therapies is a long term goal, the Special Issue attests to the fact that genome instability and DNA repair mechanisms are now centre stage in the field of neurological research. Thus we feel comfortable with the above vision, set forth in our original application in 2002.

Meetings and symposia 2006

The Special Issue described in the preceding paragraph was based on a major international meeting, hosted by the CMBN. The meeting – entitled "The First Genome Dynamics in Neuroscience Meeting" (GDN) - took place in Oslo in April 2006 and included more than 20 lecturers from abroad. The GDN event was the first international meeting to address genome instability and DNA repair in the context of neuroscience and ageing in a multidisciplinary setting. The second GDN meeting is already scheduled to be held in California, USA, in 2008.

The CMBN also organized a number of other international meetings in 2006, all of which were open for participants outside the Centre. "The first glial endfoot meeting: Physiology and pathophysiology at the brain-blood interface" was arranged in June 2006 and marked the initiation of a Storforsk project on this topic. In June 2006 CMBN researchers also arranged two other meetings: a workshop on "Databasing the brain", and the "Erling Seeberg Symposium on DNA Repair". The latter symposium commemorated the late Erling Seeberg who was one of the founding fathers of the CMBN.

October 2006 saw the organization of two other international CMBN meetings: a workshop on comparative microbial genomics and a symposium entitled "Glutamatergic mechanisms: Implications for brain disease".

A complete list of meetings and symposia is found elsewhere in this annual report.

Prizes and awards 2006

The symposium on "Glutamatergic mechanisms: Implications for brain disease" coincided with the handing out of Jahre Prizes to two CMBN scientists: Jon Storm-Mathisen (recipient of the senior prize) and Farrukh Chaudhry (recipient of the young investigator award). These prestigious prizes represent a welcome recognition of the contributions of these researchers to the field of glutamate research. The CMBN was also proud to learn that His Majesty the King's gold medal 2006 for the best doctoral thesis at the Faculty of Medicine was awarded to Tonje Davidsen at CMBN.

Other events in 2006

A new centre of excellence system – Centres for Research-based Innovation – was established in 2006. One of the appointed Centres will be headed by CMBN group leader Stefan Krauss.

On a different note, 2006 saw the establishment of the first animal-PET facility in Norway. The PET facility is run by the CMBN through Jan Bjaalie's laboratory (http://www.nesys.uio.no/pet/).

Jan Bjaalie is currently on leave of absence from the CMBN after having been appointed as the Head of International Neuroinformatics Coordinating Facility (INCF) located at the Karolinska Institute in Sweden for the period 2006 – 2007. Trygve Leergard has taken over as group leader for this period.

Ole Petter Ottersen

Tone Tønjum

It should also be mentioned that Peter Agre's term as CMBN guest professor has been renewed for 2007 – 2009. Peter Agre's active support of the Centre has been invaluable and we are glad to have him on board for a new period.

Finally we would like to take this opportunity to thank the Norwegian Research Council and all the other funding bodies that have supported the activities of the CMBN in 2006. We are also grateful to the administrative staffs of the Institute of Basic Medical Sciences and the Institute of Microbiology for their excellent assistance in administrative matters. Our thanks are extended to our host institutions: the Faculty of Medicine and Faculty of Mathematics and Natural Sciences, University of Oslo, and Rikshospitalet-Radiumhospitalet Medical Centre which have provided optimal working conditions for CMBN ever since its inception in 2002.

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MIDTERM EVALUATION

The Research Council of Norway decided in December 2006 after a comprehensive midterm evaluation to continue its support to CMBN.

The international scientific evaluation committee concluded as follows in their evaluation of CMBN (http://www.forskningsradet.no):

"The centre for Molecular Biology and Neuroscience is chaired by professor Ole Petter Ottersen, a well-known neuroscientist and there are altogether eleven principal investigators representing different areas of cellular and molecular neuroscience and molecular biology. The group leaders are as follows: professor Jan Bjaalie (Neuroinformatics), professor Magnar Bjørås, professor Niels Danbolt (Neuroanatomy), professor Arne Klungland, professor Michael Koomey, professor Stefan Krauss, professor Ole Petter Ottersen, associate professor Torbjørn Rognes, professor Johan Storm (Cellular Neurophysiology), professor Jon Storm-Mathisen (Synaptic transmission) and professor Tone Tønjum.

The ambition of this centre has been to facilitate the interaction between different research groups at University of Oslo, working with molecular techniques whether within the nervous system or in other areas. The ambition of the centre is to broaden the interaction between different subdisciplines and expand the methodology platforms available to each researcher within the centre. The overall goal has thus been to facilitate the interaction to allow each research group to apply a broader methodological repertoire with a focus on molecular (e. g. DNA repair) and cellular function as well as mechanisms to address a number of brain diseases and to find therapeutic targets at the molecular and cellular level.

Research achievements at the time of evaluation

The Centre for Molecular Biology and Neuroscience has been very active and reports no less than two hundred papers in refereed journals from July 2002 until March 2006. A large number of the articles are published in high impact journals in the different focus areas of the principal investigators extending from DNA repair to neurological diseases and mechanisms of synaptic transmission.

The different areas have been divided into work-packages led by different group leaders. The first represents ***neuroinformatics*** *(Jan Bjaalie). The centre has contributed importantly with the development of databases, extensive tool development and image registration and has taken on an international leader role in this aspect. The work-package in* ***bioinformatics*** *aims at coordinating neuro - and bioinformatics. The focus of this group has been on DNA repair, bacterial components, genome maintenance, mammalian transporter channels and the identification of single nucleotide polymorphisms. Jon Storm Mathisen and Ole Petter Ottersen have had a pio-*

*neering role in identification of the different components in **glutamatergic synaptic transmission** that is the major excitatory transmitter in the nervous system. At the same time glutamate can give rise to toxic reactions if released excessively under pathological conditions like stroke. Not only neurons but also glial cells have been found to release glutamate. The subsequent work-package on neuronal ion channels (Johan Storm) is focused on the role of different **subtypes of potassium channels**, not only during physiological conditions, but also during neurological disease. Potassium channels play a major role in the nervous system and no less than ten mutations in potassium channels have been identified and are known to lead to disease states (e. g. epilepsy). The different potassium channels are also potential targets for drugs. **DNA damage and repair** and genome instability are relevant not least in the context of neuroscience and aging. Novel DNA repair mechanisms have been identified within this work-package and are clearly of importance for neurodegenerative diseases of different kinds and its molecular mechanism. Another work-package deals with the **homeostasis** in the brain and the control of extracellular potassium, transport of water and brain oedema. It represents another major area dealt with by the chairman in interaction with Peter Agre, Nobel laureate and the discoverer of water channels. Work-package 7 (M. Koomey) deals with **meningococcal genome dynamics** is one area and the host - microbe interaction, which clearly is important for an understanding of the pathogenetic mechanisms. It is concerned with both interaction with the neuronal tissue and the glial responses. **Stem cells and repair** and memory formation are also a focus for the consortium.*

From the above follows that the centre provides a very broad field of expertise and methodology and it appears that it has managed to create an efficient and stimulating interaction between the eleven group leaders that most likely had not occurred without the formation of the Centre of Excellence. Clearly the net result is a very productive and high profile environment within a number of related and important areas of research.

The centre has a very extensive international exchange with leading research groups. The research training is of high quality and clearly of international standard. The environment has attracted a number of foreign researchers, postdocs and doctoral students and in addition a number of guest professors have worked at the centre for shorter or longer periods including Peter Agre.

Organisational and administrative aspects

The centre is coordinated by Ole Petter Ottersen with Tone Tønjum as co-director. They report to the board for the centre appointed by the President of the University of Oslo. The board in turn reports to the top management of the university and 'Rikshospitalet-Radiumhospitalet'.

Rather than creating a separate administration at the Centre of Excellence, the administrative facilities already available in the different departments have been utilised. Although being in different buildings (the distance is not too great) this form of distributed governance has apparently worked well for the centre.

The interaction between the host institution and the centre appears to have worked smoothly. The chair of the centre has previously been dean at the medical faculty. He has done a very good job as coordinator and has at the same time continued to play a major role scientifically."

HIGHLIGHTS 2006

Small animal imaging unit (PET/CT) at CMBN

Following nearly 2 years of planning and testing, new dedicated high end scanners for small animal imaging, microPET and microCAT, are now in routine use at the University of Oslo.

The decision to locate a small animal imaging unit at the Center for Molecular Biology and Neuroscience (CMBN) was made by the Faculty of Medicine in 2004. CMBN group leader, Professor Jan Bjaalie, was appointed as responsible for establishing the unit. A contract with Santax Medico AS (Denmark)/CTI Molecular Imaging (currently Siemens) (USA) was signed in 2004 and the Concorde microPET Focus 120 and Imtek microCAT II scanners were delivered in May 2005. Dr. Frode Willoch served as key advisor throughout the process of establishing the unit. He has also been in charge of the initial validation and is the lead operational scientists in the unit. Dr. Dag Sørensen at the Department of Comparative Medicine, Rikshospitalet, has provided the space for the equipment as well as valuable advice with the establishment of the animal procedures. Daily operations of the units are lead by Chief engineer, Dr. Hong Qu. Drs. Willoch and Bjaalie supervise one Ph.D. student, Trine Hjørnevik, who has an M.Sc. in Physics.

The PET radiopharmaceutical chemistry group of Associate Professor Gjermund Henriksen is closely linked to the imaging unit. All projects using tracers other than FDG are based on collaborations with Dr. Henriksen, who also takes part in the project planning and running of the experiments.

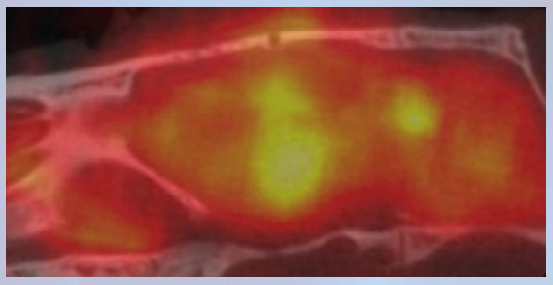
The establishment and running of the Small animal PET research are supported by the CMBN group leaders. The CMBN Director, Professor Ole Petter Ottersen, has provided continuing follow up with regard to development of new scientific concepts as well as funding initiatives. For more information, see: http://www.nesys.uio.no/pet/.

International Neuroinformatics Coordinating Facility (INCF)

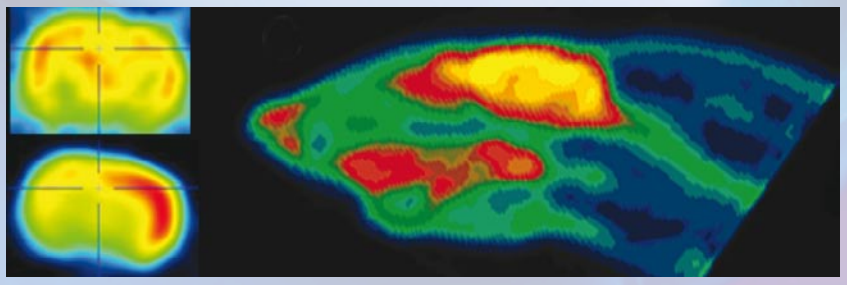
The Norwegian Node of INCF has recently been established at CMBN under coordination by group leader Johan Storm.

INCF is an international organization aimed at promoting the global development of neuroinformatics, that is, the use of methods from computer science, mathematics and statistics to strengthen neuroscience research. The main secretariat of INCF is hosted by Karolinska Institutet in Stockholm, with professor Jan G. Bjaalie as executive director. For more information, see http://www.incf.org/ .

As a first step in establishing the node we are presently informing the main neuroscience environments in Norway about INCF and the opportunities INCF offer for Norwegian neuroscience. One of the main goals in 2006 is to establish a sufficient strategy on how the INCF node should operate in Norway. In particular we want to get input on how one most efficiently can use the resources allocated to INCF Norway to strengthen the use of neuroinformatics methods.



Combined PET/CT examination of rat brain showing focally increased uptake of 18F-fluoro deoxyglucose metabolism after inoculation with glioma cells.



PET examinations showing changes in 18F-fluoro deoxyglucose uptake in response to sensory stimulation.

AWARDS AND DOCTORAL DEGREES

Awards 2006

Anders Jahre's awards to Jon Storm-Mathisen and Farrukh Chaudhry
Professor and group leader Jon Storm-Mathisen and CMBN guest professor Farrukh Chaudhry were awarded Anders Jahre's prizes for medical research in 2006. The prizes are awarded for their research on signalling molecules in the brain and on protein structures, and are the most prominent biomedical research awards in the Nordic countries.

Farrukh Chaudhry *Jon Storm-Mathisen*

Gold medal to Tonje Davidsen
The University of Oslo decided that His Majesty the King's gold medal 2006 for the best doctoral thesis at the Faculty of Medicine be awarded to Tonje Davidsen at CMBN. The doctoral degree was supervised by CMBN co-director and group leader Tone Tønjum.

Tonje Davidsen

Doctoral degrees 2006

Petter Angell Olsen defended his PhD thesis with the title: "Targeted sequence alteration in the genomes of mammalian cells mediated by oligonucleotides". The candidate was supervised by group leader Stefan Krauss.

Fulvio Celsi defended his PhD thesis at The University of Tor Vergata (Roma) with the title; "Calcineurin role in pathogenesis of Alzheimer's Disease". The candidate was co-supervised by CMBN director and group leader Ole Petter Ottersen and CMBN researcher Reidun Torp.

Runhild Gammelsæter defended her PhD thesis with the title: "Amino acid signaling in islets of Langerhans". The candidate was supervised by senior researcher Vidar Gundersen.

Cecilia Løvold defended her PhD thesis with the title: "Covalent modifications of Neisseria gonorrhoeae Type IV pili with phosphoethanolamine and phosphocholine: Roles of the PptA protein and ancillary factors". The candidate was supervised by group leader Michael Koomey .

Elise Rundén Pran defended her PhD thesis with the title: "Intra- and extracellular signaling pathways underlying cell death in hippocampus". The candidate was supervised by CMBN director and group leader Ole Petter Ottersen.

Anna Thoren defended her PhD thesis at The Göteborg University with the title: "Astrocyte metabolism following focal cerebral ischemia". The candidate was co- supervised by CMBN Director and group leader Ole Petter Ottersen.

Jo Kristian Utvik defended his PhD thesis with the title: "Protein interactions at the glutamate synapse". The candidate was supervised by CMBN director and group leader Ole Petter Ottersen. Svend Davanger acted as co-supervisor.

NETWORKS

Gaustad Neuroscience Network (GNN), which was established at the initiative of CMBN, is a network that aims at linking basic science and clinical research at Gaustad. This initiative is a multidisciplinary action and addresses all aspects of neuroscience represented on the campus. The goal is to heighten the awareness of activities, competence and resources available locally, in order to elicit new collaborations, and to increase the output from ongoing research. The ambition is that GNN should foster a neuroscience research environment at the highest international level. New funding will have to be generated for GNN research activities, and in this context it is also notable that the Research Council of Norway has established a new funding source, NevroNor, which will support neuroscience research at the national level.

CMBN contributes to GNN by organizing meetings and providing financial and logistical support for workshops and meetings. CMBN also covers a 20% position for a researcher that acts as a liaison officer between the clinical and basic research departments. GNN contributions and activities in 2006 included the organization of the globally attended Genome Dynamics in Neuroscience (GDN) meeting in April 2006, participation at the NCoE / WIRED meeting in June 2006 and hosting a seminar jointly organized between Rikshospitalet-Radiumhospitalet Medical Centre and Ullevål University Hospital at Gaustad.

International networks

Nordic Centre of excellence (NCoE) for Research in Water Imbalance Related Disorders (WIRED). Coordinator is CMBN director Ole Petter Ottersen. This Network is composed of four research teams from Norway, Sweden and Denmark plus an associated node in Finland.

Nordic Centre of excellence (NCoE) in Neurodegeneration, with CMBN group leaders Johan Storm and Arne Klungland as project partners. This Network is composed of 11 research teams from Sweden, Finland, Denmark and Norway.

NorFa Network of stem cell and regenerative medicine with CMBN group leader Stefan Krauss as coordinator.

EU project under the Sixth Framework Program **(Specific Targeted Research or Innovation Project, STREP)** on "Glutamate Receptor Interacting Proteins As Novel Neuroprotective Targets (GRIPANNT)" coordinated by the director of CMBN Ole Petter Ottersen. This EU network is composed of 10 partners from Poland, France, England, Denmark and Norway.

EU project under the Sixth Framework Program, Integrated Project "DNA damage response and repair mechanisms", with CMBN group leaders Magnar Bjørås, Arne Klungland, Torbjørn Rognes as partners.

EU project under the Sixth Framework Program **(STREP)** on "Targeted sequence alteration". Coordinator is CMBN group leader Stefan Krauss.

EU project under the Sixth Framework Program **(STREP)** on "Effect of genetic variation in *Mycobacterium tuberculosis* on vaccine escape and the acquisition of drug resistance (TBadapt)" with CMBN assistant director and group leader Tone Tønjum as partner. This EU network is composed of 11 partners from the Netherlands, United Kingdom, France, South Africa, Mexico, Vietnam and Norway.

EU project under the Sixth Framework Program **(ESF "Eurostells")** international stem cell network. Coordinator is CMBN group leader Stefan Krauss.

EU project under the Fifth Framework Program **(Marie Curie Training Site)** in: Basic mechanisms of aminoacid neurotransmission (BAMAN). Coordinator is CMBN group leader Jon Storm-Mathisen.

EU project under the Sixth Framework Program **(Marie Curie actions – Host fellowships for Early Stage Research Training)** in: Cooperation in Research and Training for European Excellence in the Neurosciences (CORTEX). Partner is director of CMBN Ole Petter Ottersen.

GlobHel "Tuberculosis in the 21st century", global network on advanced tuberculosis research sponsored by the Research Council of Norway. Co-partner is assistant director of CMBN Tone Tønjum, on the impact of genome instability.

FEMS - Secretary General for the Federation of European Microbiology Societies (FEMS) for 2006-2009 is held within CMBN (T. Tønjum).

The ***Chief Editorship of "Neuroscience"*** - the official journal of the International Brain Research Organization (IBRO) - lies within the Centre (Ole P. Ottersen).

EDUCATION AND INTERACTION ACTIVITIES

Central elements of the Centre's plan of activities are teaching and academic interactions. The plan also includes internal cooperation between the 11 groups of researchers as well as the further development of the Centre's relations with external partners.

Research courses and lectures

As part of the CoE Programme, the CMBN has undertaken to provide teaching for PhD students and post-doctoral fellows. The Centre is part of the Research School ("Forskerskole") curriculum established by the University of Oslo in 2004. The CMBN Research school is headed by group leader Tone Tønjum. The following seminars were held in 2006:

The second Norwegian Transgenic Animal Forum was arranged at Tyrifjord Hotel, Vikersund, 23-24 March 2006.

The primary goal of the forum was to strengthen the scientific collaboration in the field of mouse transgene technology and to discuss how this technology should be made available to the biomedical research community in Norway.

EDUCATION AND INTERACTION ACTIVITIES

The First Genome Dynamics in Neuroscience (GDN) meeting took place on 26 - 29 April 2006 at The National Hospital.

The Genome Dynamics in Neuroscience (GDN) meeting in April 2006 was the first international meeting to address genome instability and DNA repair in the context of neuroscience and ageing in a multidisciplinary setting. Mechanisms for genome variation, adaptation and maintenance are a necessity to ensure cellular fitness and survival in changing environments. The objective of the meeting was to highlight key aspects of DNA damage and repair in ageing and the pathogenesis of neurological disease, and to improve our understanding of how nerve cells communicate in the healthy and diseased brain. The topics addressed are relevant for neurological pathogenesis, genome instability and maintenance, stem cell biology, brain development, prokaryotic model systems and synaptic communication. The long-term goal is to identify new approaches for the treatment of brain disease and age-related neurological impairment. Added value from the meeting materialized in the production of a Special issue entitled "Genome dynamics in neuroscience" in the IBRO journal Neuroscience, encompassing 25 reviews and original articles by outstanding scientist from all parts of the world.

The Erling Seeberg Symposium on DNA Repair took place in Bodø and Henningsvær in Lofoten from 28 May to 2 June, 2006.

One of the motivations for organizing this meeting was to honour Erling Seeberg. He had made many important and novel contributions to the field of biology in general and DNA repair and mutagenesis specifically. Erling Seeberg played a central role in the establishment of CMBN in 2002.

EDUCATION AND INTERACTION ACTIVITIES

The first glial endfoot meeting, Physiology and pathophysiology at the brain blood interface, took place in Oslo, 6-7 June 2006.
The meeting was organized jointly by WIRED and the Centre for Molecular Biology and Neuroscience (www.cmbn.no/wired), The meeting highlighted recent advances in our understanding of the physiology and pathophysiology of astrocytes, with focus on the perivascular endfeet and their role in regulating exchange of water, gases, and metabolites at the brain blood interface.

Minisymposium: Neuroendocrine Signalling by Amino Acids - New Deal in Diabetes? Oslo 14 June
Professor Dr. Gudrun Ahnert-Hilger from AG Funktionelle Zellbiologie, Charité-Universitätsmedizin Berlin, Germany , held her lecture on the topic:

Regulation of vesicular transmitter uptake by heterotrimeric G proteins

Professor Dr Patrik Rorsman from Oxford Centre for Diabetes, Endocrionology and Metabolism (OCDEM), University of Oxford, UK, held his lecture on the topic:

GABA and the control of pancreatic islet function: studies in man and rodents

The second Databasing the brain workshop took place on 25-27 June 2006 at the Soria Moria conference center in Oslo.
The overall objective of the workshop was to accelerate existing research and development efforts in the field of neuroscience databasing. The workshop brought together scientists in the field of brain databasing, neuroscientists, representatives of SMEs, as well as journal editors and other representatives of journals.

A Comparative Microbial Genomics Workshop was organized in Oslo on 16-20 October 2006 by associate professor David W Ussery from the Centre for Biological Sequence Analysis (CBS) at the Technical University of Denmark (DTU), and others.
The workshop was designed to enable participants to use comparative genomic tools through lectures and hands-on practicals to extract biological meanings and discover novel genes from the vast amount of genomic data and solving problems of their research interest. The workshop also served as a platform for participants to establish multidisciplinary collaborations in comparative genomics research among various groups of scientists and researchers at national and international level.

The First Norwegian Microbiology Meeting for junior scientists was arranged at Geilo on 22-24 October 2006.
The NoMi-06 meeting was the first in a biannual series of meetings that seeks to gather junior scientists, post-docs, and Ph.D. students working in Norwegian institutions and companies in the area of microbial biology. This first meeting was limited to 60 participants from all regions of Norway and was organized by the FUGE platform CAMST (Consortium of Advanced Microbial Science and Technology) and the University of Oslo.

CMBN International Symposium & Jahre Lectures was held in Oslo 12-13 October
The symposium Glutamatergic Mechanisms: Implications for Brain Disease was arranged in Oslo on 12-13 October. The Jahre lectures and award ceremony took place the same days.

In addition to seminars, CMBN also contributes to the Faculty of Medicine's PhD educational program, with group leader Arne Klungland who is responsible for two one week laboratory courses ("Basic Methods in Molecular Biology") for PhD students, including national and international students.

CMBN PhD group activities 2006

The PhD student group tries to meet a couple of times each semester, to discuss science, inform about the PhD programme and new acquisitions of equipment and technologies at CMBN. The group also promotes collaborative projects within the Centre, learn about each others work, and last, but not least engage in various kinds of social activities (http://www.cmbn.no/phd/). All the CMBN departments have hosted a group meeting after the PhD student group's establishment.

In March 2006 Arne Klungland, Professor at the department of Molecular Biology, gave a talk with the title "Transgenic or gene targeting?" In May, Willy Fjeldskaar, Professor and chief scientist at the International Research Institute of Stavanger (IRIS), visited us to give a talk entitled "Is Darwin's theory a good explanation for the nature's complexity?" In October we had invited Professor Sissel Rogne from The Norwegian Biotechnology Advisory Board. The topic of her talk was the proposed law on Norwegian stem cell research, giving comments and trying to define the terms research, method development, life, moral, ethics, chimeras, human/animal, stem cells and their potential and serious disease. These three scientific meetings were held in the department of Molecular Biology at the Rikshospitalet-Radiumhospitalet Medical Centre. After the talks we had discussions and refreshments were served.

The PhD students also participated in CMBN lectures and seminars, and some of us joined the CMBN team in Holmenkollstafetten. For 2007 we hope to continue the scientific meetings throughout the year, and also arrange some social activities. The organization committee welcomes new members.

Guest Professors

The recruitment of "Guest Professors" is an important element in the Centre's strategy for academic cooperation. This cooperation is funded both through the Centre's CoE grant and through external funds for which special applications are made for appropriate purposes. In 2006 the following four CMBN "Guest Professors" were formally appointed:

Peter Agre, Professor and Nobel Prize winner in Chemistry, 2003, Johns Hopkins University, Baltimore, USA, now at Duke University. Funded by CMBN.

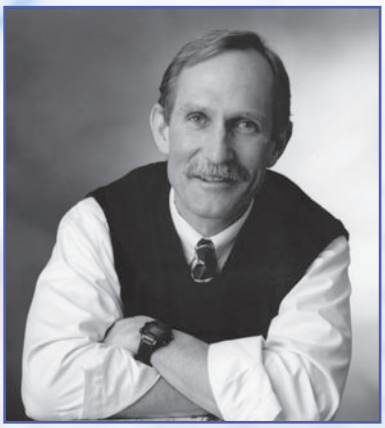
Vilhelm Bohr, Chief of Laboratory of Molecular Genetics, National Institute on Aging, NIH, Baltimore. Funded by CMBN.

Farrukh A. Chaudhry, Associate professor / group leader at the Biotechnology Centre, University of Oslo. Funded by CMBN.

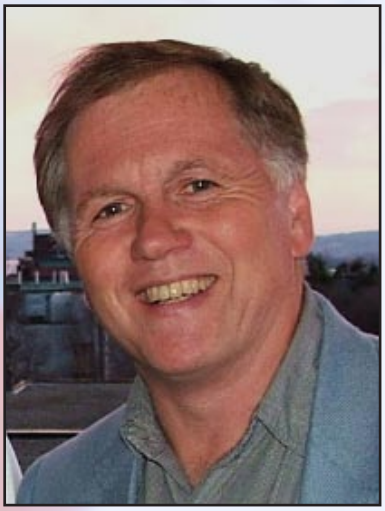
Pål Falnes, Professor at the Institute of Molecular Bioscience, University of Oslo. Funded by CMBN.

Shankar Subramaniam, Professor, University of California at San Diego & San Diego Supercomputing Center. Funded by CMBN.

Dave Ussery, Associate professor in the Centre for Biological Sequence Analysis, Technical University of Denmark. Funded by EMBIO at the University of Oslo.



Peter Agre



Vilhelm Bohr

CMBN seminars/guest lecturers

Altogether, 14 CMBN seminars were held in 2006 with high-profile researchers from abroad as specially invited lecturers. These guest lectures were arranged on the initiative of the Centre management or group leaders. CMBN seminars are open to all and are widely announced.

Postdoc **Ken Howard** at the Department of Molecular Biology, University of Aarhus, gave his guest lecture on Thursday, 12 January 2006 on the topic: ***Small interfering RNA delivery and gene silencing using nanocarrier systems***

Professor **Vilhelm A. Bohr**, chief, Laboratory of Molecular Gerontology, National Institute on Aging, NIH, US, gave his guest lecture on Wednesday, 25 January 2006 on the topic: ***Oxidative DNA damage processing and changes with aging***

Professor **Bernd Epe,** Institute of Pharmacy, University of Mainz, Germany, gave his guest lecture on Thursday, 9 February 2006 on the topic: ***Endogenous oxidative DNA base damage and its consequences***

Professor **Valina Dawson**, Department of Neurology, The Johns Hopkins University School of Medicine, USA, gave her guest lecture on Tuesday 28 February 2006 on the topic: ***Genetic Clues to Unravel the Mystery of Parkinson's Disease***

Chris Tang, Imperial College, London, UK, gave his guest lecture on Tuesday 2 May 2006 on the topic: ***Interactions of N. meningitidis with the complement system***

Kim Q Do, PhD, privat-docent, Center for Psychiatric Neuroscience, Lausanne University, Switzerland, gave her guest lecture on Tuesday 9 May 2006 on the topic: ***Schizophrenia: redox dysregulation as vulnerability factor; from basic to clinical perspectives***

James Fallon, professor of Anatomy and Neurobiology, University of California, USA, gave his guest lecture on Thursday 24 August 2006 on the topic: I***maging Genetics and the Neuroanatomy of Affective and Thought Disorders***

Dr **Manuel S. Malmierca**, Laboratory for the Neurobiology of Hearing, The Institute of Neuroscience of 'Castilla y Leon' (INCyL), Faculty of Medicine, University of Salamanca, Spain, gave his guest lecture on Tuesday 25 July 2006 on the topic: The inferior colliculus: ***A key centre for auditory processing in the midbrain***

Randi G. Syljuåsen, Institute of Cancer Biology and Centre for Genotoxic Stress Research, Danish Cancer Society, Copenhagen, Denmark, gave her guest lecture on Tuesday 29 August 2006 on the topic: ***Cell cycle checkpoints induced in the absence and presence of ionizing radiation***

Prof **Jean-Pierre Changeux**, Collège de France and l'Institut Pasteur, France, gave his guest lecture on Wednesday 27 September 2006 on the topic: ***The role of brain nicotinic receptors in reward and cognition***

Philip Beart, Howard Florey Institute, University of Melbourne, Australia, gave his guest lecture on Tuesday 12 September 2006 on the topic: Astrocytes and neuroprotection: ***mechanistic insights into the roles of glutamate transporters and hypoxia-inducible factor (HIF)***

Keiko Shimamoto, Suntory Institute for Bioorganic Research, Osaka, Japan, gave his guest lecture on Tuesday 12 September 2006 on the topic: ***Synthesis and Characterization of Novel Blockers to Probe Glutamate Transporter Functions***

Assistant Research Professor **Fan Meng PhD**, Microrarray Laboratory, Psychiatry Department and Molecular and Behavioral Neuroscience Institute, University of Michigan, gave two guest lectures on Thursday 28 September 2006 on the topics: ***First lecture: Knowledge-based analysis of genome-wide SNP scanning data and second lecture: GeneChip data analysis: the trick is in the probe sets***

Dr. **Lars Juhl Jensen**, staff scientist at EMBL in Heidelberg, gave his guest lecture on Wednesday 25 October 2006 on the topic: ***Cross-species data integration***

The Centre's lecture series for 2006 was supplemented by seminars under the auspices of affiliated units in the two host institutions (UiO and RR-HF). In addition there were open lectures under the auspices of each individual group at the Centre.

CMBN scientific retreat

The annual CMBN retreat was held at Hafjell. The Centre and its 11 research group were present with nearly 100 participants from the scientific, technical and administrative staff.

This annual CMBN retreat with lectures, workshops and discussions at Hafjell contributed to enhanced awareness and interactions between the research groups, not the least promoted by very interactive poster sessions (organized as guided tour / tutorials) and discussions.

COMMERCIALIZATION

In accordance with the agreements relating to the Centre, the commercialisation of research results emanating from the Centre is an important element in its future funding. The CMBN commercialization portfolio consisted in 2005 of two projects supported by Birkeland Innovation, which is the Technical Transfer Office (TTO) owned by The University of Oslo. Our Centre is also a partner in two spin off companies.

Sencel Bioinformatics founded in June 2001.The Company provides superior software tools to aid in genetic and genomic research and diagnostics. The name of the company stems from the mission to make **sen**se of genetic data at an ac**cel**erated speed (www.sencel.com)

SENCEL™

SiRNASENSE A/S founded in December 2004. This is a company that aims at developing Anti-sense Therapeutics, RNA/SiRNA for pharmaceutical therapeutics.

siRNAsense

Stem Cell Based Tumor Therapy (Centre for Research-based Innovation). The main objective for the Centre for Research-based Innovation (CRIs) is to enhance the capability of the business sector to innovate by focusing on long-term research based on forging close alliances between research-intensive enterprises and prominent research groups. The Centre will be headed by CMBN group leader Stefan Krauss.

MEDIA COVERAGE

The Centre has invested a great deal in popular-scientific publicising – both in Norway and abroad. A survey can be found on the Centre's Web page www.cmbn.no. The Centre's research has on numerous occasions been referred to in the main Norwegian daily newspapers. CMBN has made active contributions to the "Research Days" (sponsored by the Research Council) and participated in a number of radio and TV programmes.

CMBN's web pages are continually updated with media events relating to the Centre and our different activities (web page responsible: CMBN group leader Torbjørn Rognes). Our media contact is CMBN group leader Jon Storm-Mathisen.

After having published an article in Nature (Ragnhildur Káradóttir, Pauline Cavelier, Linda H. Bergersen and David Attwell (2005) NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. Nature, 438, 1162-1167), Linda H. Bergersen told Uniforum (January 2006) that she felt like she had won the Olympic medal in 4x100 meters.

Photo: Martin Toft | Uniforum

PUBLICATIONS

JANUARY 06 – DECEMBER 06

Abstracts not included

High impact papers (impact factor >6.0, according to ISI 2005) are indicated by *

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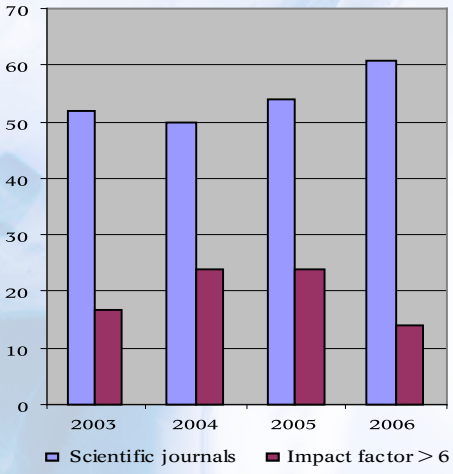

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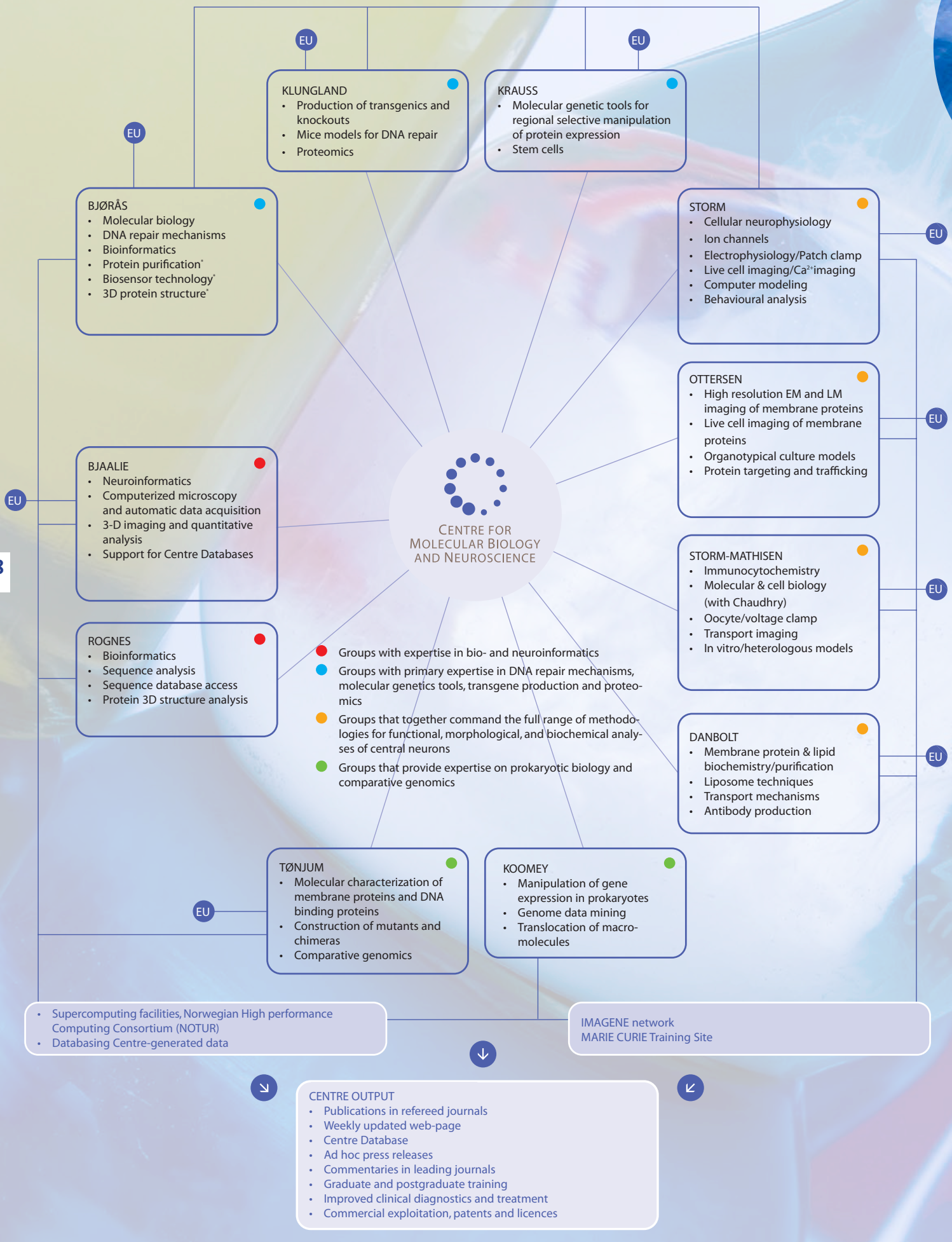
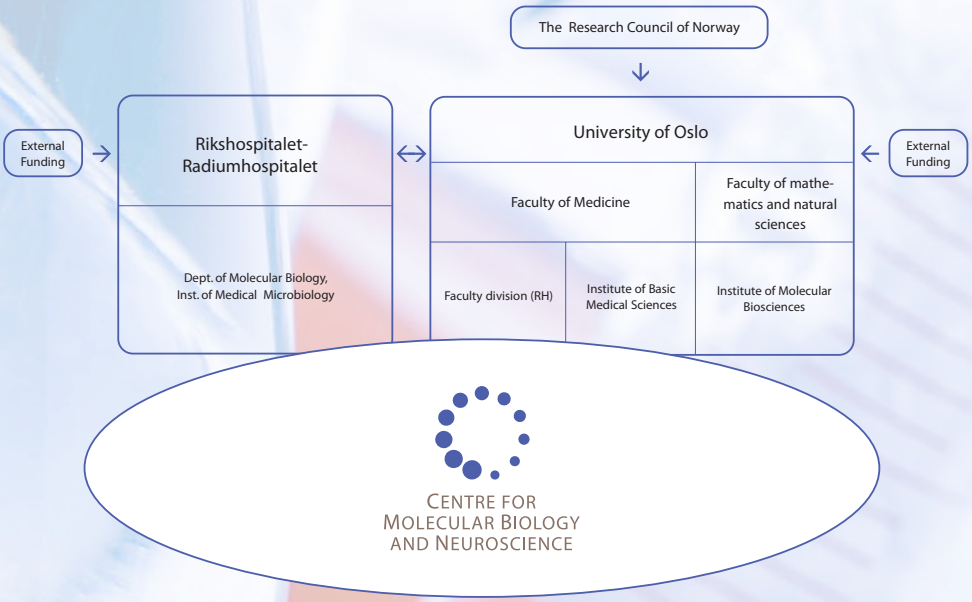

EU
EU
KLUNGLAND
• Production of transgenics and knockouts
• Mice models for DNA repair
• Proteomics
KRAUSS
• Molecular genetic tools for regional selective manipulation of protein expression
• Stem cells
EU
BJØRÅS
• Molecular biology
• DNA repair mechanisms
• Bioinformatics
• Protein purification*
• Biosensor technology*
• 3D protein structure*
STORM
• Cellular neurophysiology
• Ion channels
• Electrophysiology/Patch clamp
• Live cell imaging/Ca2+imaging
• Computer modeling
• Behavioural analysis
EU
OTTERSEN
• High resolution EM and LM imaging of membrane proteins
• Live cell imaging of membrane proteins
• Organotypical culture models
• Protein targeting and trafficking
EU
EU
BJAALIE
• Neuroinformatics
• Computerized microscopy and automatic data acquisition
• 3-D imaging and quantitative analysis
• Support for Centre Databases
CENTRE FOR MOLECULAR BIOLOGY AND NEUROSCIENCE
STORM-MATHISEN
• Immunocytochemistry
• Molecular & cell biology (with Chaudhry)
• Oocyte/voltage clamp
• Transport imaging
• In vitro/heterologous models
EU
ROGNES
• Bioinformatics
• Sequence analysis
• Sequence database access
• Protein 3D structure analysis
Groups with expertise in bio- and neuroinformatics
Groups with primary expertise in DNA repair mechanisms, molecular genetics tools, transgene production and proteomics
Groups that together command the full range of methodologies for functional, morphological, and biochemical analyses of central neurons
Groups that provide expertise on prokaryotic biology and comparative genomics
DANBOLT
• Membrane protein & lipid biochemistry/purification
• Liposome techniques
• Transport mechanisms
• Antibody production
EU
TØNJUM
• Molecular characterization of membrane proteins and DNA binding proteins
• Construction of mutants and chimeras
• Comparative genomics
KOOMEY
• Manipulation of gene expression in prokaryotes
• Genome data mining
• Translocation of macromolecules
EU
• Supercomputing facilities, Norwegian High performance Computing Consortium (NOTUR)
• Databasing Centre-generated data
IMAGENE network
MARIE CURIE Training Site
CENTRE OUTPUT
• Publications in refereed journals
• Weekly updated web-page
• Centre Database
• Ad hoc press releases
• Commentaries in leading journals
• Graduate and postgraduate training
• Improved clinical diagnostics and treatment
• Commercial exploitation, patents and licences



ABOUT CMBN AND THE GROUPS

The Centre for Molecular Biology and Neuroscience (CMBN) at the University of Oslo (UiO) and Rikshospitalet-Radiumhospitalet Medical Centre (RR) is a Norwegian Centre of Excellence, appointed by the Research Council of Norway. The Centre`s main activities are located at Gaustad, in two adjacent buildings belonging to the University and RR, respectively.

Objectives

The Centre shall take on a leading role in elucidating the role of DNA repair and genome maintenance mechanisms in preventing neurological disease and brain ageing. The Centre will develop and apply stem cell technology and targeted repair to broaden the range of therapeutic strategies in neurological disease. The centre will also investigate the processes that are upstream of DNA damage in nerve cells and will explore the excitotoxic hypothesis which holds that DNA damage may be caused by over-stimulation of glutamate receptors and subsequent formation of oxygen radicals. Progress in this field will require a better understanding of the function and molecular organization of the glutamate synapse.

Management and organization

The Centre was in 2006 led by Ole Petter Ottersen (Director) and Tone Tønjum (Assistant Director). Peder Heyerdahl Utne was the administrative leader. The Centre has a Steering Group who meets on a regular basis. This group consists of the eleven group leaders of the consortium.

For 2006 the Centre's activities were mainly located in DOMUS MEDICA and the Research Building at RR, at Gaustad. The groups led by Krauss, Koomey, and Rognes are located on other premises in and around the University Campus.

The board

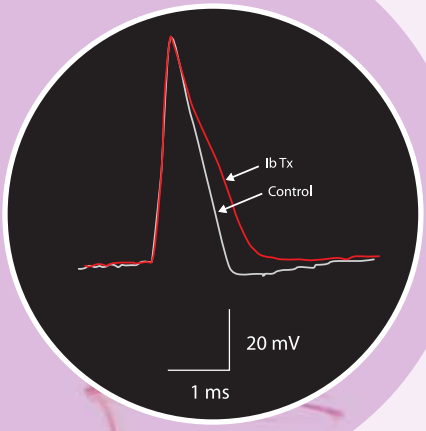
The Board is responsible for ensuring that CMBN is developed in accordance with the current research plan. The members are:

Prof. Ole M. Sejersted,
University of Oslo (Chairman)
Director Prof. Olli A. Jänne,
Biomedicum Helsinki, Finland
Director Per Morten Vigtel,
Norsk Investorforum
Strategy Director Stein Vaaler,
Rikshospitalet-Radiumhospitalet
Head of Department Peter Gaustad,
Rikshospitalet-Radiumhospitalet
Professor Borghild Roald,
University of Oslo

Research groups

The Centre consists of 11 research groups at the University of Oslo (UiO) and Rikshospitalet-Radiumhositalet Medical Centre. In 2006 Trygve Leergaard was appointed as group leader with responsibility for NeSys – Neural systems and grahics Computing Laboratory, during the leave of absence of Jan G. Bjaalie. In total, more than 157 people are involved in the research at CMBN. The 11 groups of the CMBN are presented on the following pages.

Laboratory of Cellular Neurophysiology and Ion channel function



Action potentials in a hippocampal pyramidal neuron, before and after blockade of BK- type potassium channels.

About

Our group is interested in brain function, from molecules to behavior. We study fundamental principles and mechanisms of neuronal signalling in the mammalian brain, and the roles of ion channels in behaviour, brain function, and disease. We focus on the functions of ion channels, in particular K^+ channels, in central neurons and circuits, mainly in the hippocampus and cerebral cortex.

Methods: Electrophysiological and optical recordings in brain slices and *in vivo*, molecular genetic and pharmacological manipulations, computational modelling, and behavioural tests.

Challenges

- To determine the functional roles and interplay of multiple signaling mechanisms and ion channel types within different neuronal compartments and within the entire neuron.
- To elucidate functional roles of specific neuronal populations, signaling mechanisms and ion channel types, in active neuronal networks, and in the brain of behaving animals.
- To elucidate the roles of neuronal signaling mechanisms in ageing and neurological disease, including neurodegenerative and ischemic disorders, epilepsy, and memory disorders.

Projects

- The roles of Kv7/KCNQ/M- and h/HCN-type K^+ channels in neuronal signalling, brain oscillations, synaptic plasticity, cognitive functions and epilepsy.
- The roles of Ca^{2+}-activated K^+ channels (BK and SK channels) in neuronal signalling, synaptic plasticity, cognitive functions, motor control, epilepsy and neuroprotection.
- The roles of voltage-gated ion channels in neuronal signalling, synaptic plasticity, learning and memory.
- Changes in neuronal signalling during ontogenetic development and ageing.

Recent achievements: Discovered that Kv7/M/KCNQ-type K^+ channels are present in the perisomatic region but not in the apical dendrites of hippocampal pyramidal neurons (Hu et al., *J. Neuroscience*, 2007). Discovered that the persistent sodium current, INaP, paradoxically amplifies after hyperpolarizations and reduces the frequency (f/I) gain, and strongly modulates spike timing (Vervaeke et al., Neuron 2006); that Kv7/M/KCNQ-type K^+ channels but not SK channels are essential for excitability control in hippocampal neurons (Gu et al., *J Physiol*, 2005); that Kv7/M/KCNQ-type K^+ channels are essential for spatial learning and prevention of epilepsy (*Nature Neuroscience* **8**: 51-60, 2005), that $K_{Ca}1$/BK-type K^+ channels are essential for cerebellar learning and motor control (*Proc Natl Acad Sci USA* **101**: 0474-8, 2004), the role of postsynaptic voltage-gated K^+ channels in regulation of synaptic plasticity (LTP) and integration (*Proc Natl Acad Sci USA* 99:10144, 2002); that Kv7/M/KCNQ-type K^+ channels are essential for intrinsic theta resonance in hippocampal neurons (*J Physiol* 545:783, 2002).

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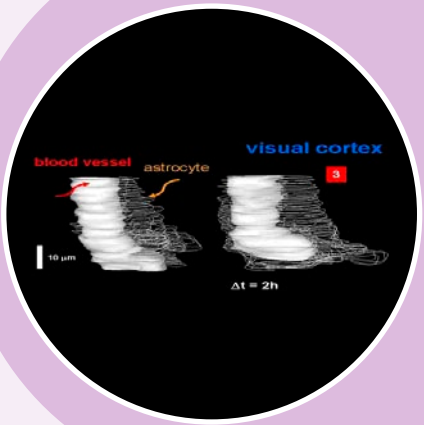
Laboratory for Molecular Neuroscience

About

The Laboratory for Molecular Neuroscience investigates molecular mechanisms involved in the development of acute and chronic neurodegenerative disease, with a focus on the role of glutamate excitotoxicity. It aims at unravelling the molecular basis for cell death and edema development in stroke and other neurological conditions, and explores the pathophysiology of Alzheimer's disease and temporal lobe epilepsy. Long term goals are to identify new molecular targets for neuroprotective strategies in stroke and other conditions involving glutamate excitotoxicity and to unravel the physiological and pathophysiological roles of astrocyte endfeet.



Swelling of astrocyte, monitored in a living mouse 2h after induction of hypo-osmotic stress. Transcranial multi photon in vivo imaging (courtesy of Gabriele Nase and Johannes Helm).

Challenges

Neurology continues to lag behind other disciplines when it comes to the range and efficacy of therapeutic strategies. In particular, common neurological conditions such as stroke, Alzheimer's disease, and other acute or chronic neurodegenerative diseases call for new therapeutic strategies. Several of these conditions are particularly prevalent among the elderly and will constitute a growing health concern as the population ages. The challenge is to identify new principles of treatment for these diseases.

Projects

- Assessing the role of water channel molecules (aquaporins) in the development of brain edema and in the regulation of ion homeostasis in brain extracellular fluid.
- Exploration of the composition and function of the protein complexes that interact with glutamate receptors and that mediate downstream signalling from these.
- Unravelling the synaptic expression of kainate, NMDA, and AMPA receptors and the mechanisms responsible for their turnover.
- Identification of mechanisms underlying loss of glutamate homeostasis in temporal lobe epilepsy.
- Exploration of mechanisms involved in the formation of beta-amyloid in aging and Alzheimer's disease

Recent achievements: Resolving modes of NMDA and AMPA receptor expression in hippocampal spine synapses (Nature Neuroscience 2:618-624, 1999). Identification of principles underlying expression and regulation of the water channel aquaporin-4 in the CNS (J Neurosci 17:171-80, 1997; J Neurosci 21:3045-51, 2001; PNAS 98:14108-13, 2001). Showing that removal of perivascular aquaporin-4 protects against development of postischemic edema and delays K^+ clearance from the extracellular space (PNAS 100:2106-11, 2003; PNAS, 100:13615-20, 2003, Nature Reviews Neuroscience, 4:991-1001, 2003). Identification of neuronal plasma membrane microdomains that colocalize beta-amyloid and presenilin (Neuroscience, 120:291-300, 2003). Demonstrating loss of glutamine synthetase and perivascular aquaporin-4 in patients with temporal lobe epilepsy (Lancet, 363:28-37, 2004; PNAS 102:1193-8, 2005). Unravelling the molecular organization and function of astrocyte endfeet (PNAS 102: 8030-5, 2005; PNAS 103: 13532 – 6, 2006).

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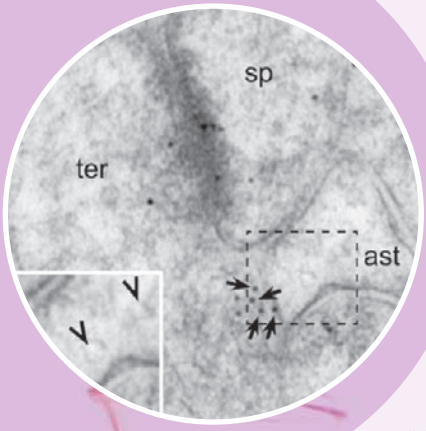
The Synaptic Neurochemistry Laboratory



Electron micrograph showing NR2B signalling gold particles at the synapse as well as in extrasynaptic membranes (arrows) of nerve terminals (ter) making asymmetric synapses with dendritic spines (sp) in the dentate molecular layer. NR2B particles face astrocytic processes (ast) that contain SLMVs. NR2B is in close proximity to astrocytic SLMVs. Inset, higher magnification showing NR2B gold particles and astrocytic SLMVs (arrowheads). Scale bars, 100 nm. Nature Neuroscience March 2007

About

Main interests are the mechanisms underlying synaptic transmission: localization, transport, synthesis, release, action and breakdown of neurotransmitters (glutamate, aspartate, GABA, glycine, monoamines, acetylcholine). These mechanisms are studied in normal and pathological conditions, and during ontogenetic development and ageing.

Challenges

Recent research by our group has opened possibilities for studying in depth aspects of nervous system functions in health and disease. An important aspect is how nerve endings provide glutamate for synaptic release and how they recover released glutamate for reuse. Thus the molecular identification and characterization of glutamine transporters, SN (Cell 1999, EMBO J 2001, Eur J Neurosci 2002, Glia 2003, J Am Soc Nephrol 2005) and SA/SAT (PNAS 2000, J Neurosci 2002, J Cell Biol 2002), and the ultrastructural localization of monocarboxyltate transporters (Cereb Cortex 2005) provide new approaches to understanding synaptic function. The identification of proteins, VGLUT1-3 (Neuron 2001, PNAS 2002), that pump glutamate into synaptic vesicles allows the packaging of the transmitter to be characterised (J Comp Neurol 2004, 2006) and modified (Science 2004). The observation that even astrocytes (Nature Neurosci 2004, 2007) and neuroendocrine cells (J Cell Sci 2004) can release neurotransmitter amino acids in a way resembling synaptic release, together with findings that glutamate and other neuroactive substances can be co-released from nerve endings (Eur J Neurosci 2003, Molec Neurosci 2004), and that oligodendrocytes have NMDA receptors (Nature 2005), suggests novel ways of intercellular communication.

Projects

- The role of glutamine, and other metabolic precursors of glutamate, for keeping up synaptic release. Transporters and metabolising enzymes are located immunocytochemically and their functional roles studied in oocytes and cultured cells by artificial expression, and in animals with modified or blocked expression of the specific genes.

- Interplay of glutamate with e.g. aspartate, GABA or glycine at brain synapses and endocrine cells. Localisation of the amino acids and their transporters, receptors and enzymes in normal and experimentally modified animals, ie animal models of neurological disease (e.g. epilepsy), including knock-out mice.

- Synaptic changes during ontogenetic development and in animals with deficient DNA repair.

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The Neurotransporter Group

The distribution of glutamate transporter proteins

About

The Group studies how transporter proteins (in normal and diseased brains of different ages) modulate the extracellular spatiotemporal concentration profiles of excitatory (glutamate and aspartate) and inhibitory (GABA and glycine) transmitter amino acids. The transporters studied are those able to transport aspartate, GABA, glutamate, glycine and monoamines across brain plasma membranes. These include the glutamate (EAAT1-5), GABA (GAT1-4), glycine (GLYT1-2), dopamine (DAT) and dicarboxylate (SDCT2) transporters as well as the glutamate-cystine exchanger and their anchoring and regulatory proteins.

Challenges

The human genome contains about 300 different transporter protein genes. Many of the encoded transporters, including those for glutamate, are subject to sophisticated dynamic regulation, and are also ion channels in addition to being transporters. Thus, the transporters appear to have more refined functions than just being pumps, but these functions are poorly understood. The overall aim of the Group is to determine the roles of the individual transporter subtypes in order to better understand normal physiology and disease, and to uncover new therapeutic opportunities. Disturbed control of extracellular glutamate appears to be an important factor, directly or indirectly, in all neurological disorders as well as in drug abuse and major psychiatric disorders (e.g. schizophrenia), as a consequence of the abundance of glutamate, the ubiquitous presence of glutamate receptors, and the interplay between glutamate, oxidation and energy metabolism (for review see: Danbolt, 2001: Prog. Neurobiol).

Projects

- Production of suitable tools (including antibodies) and model systems (including gene modified animals)
- Determination of transporter distributions and densities around select synapses in normal adult brains and how these parameters change during development, ageing, drug use and disease
- Computer modelling of transmitter release, diffusion, removal and receptor activation
- Transporter protein purification, reconstitution and crystallisation

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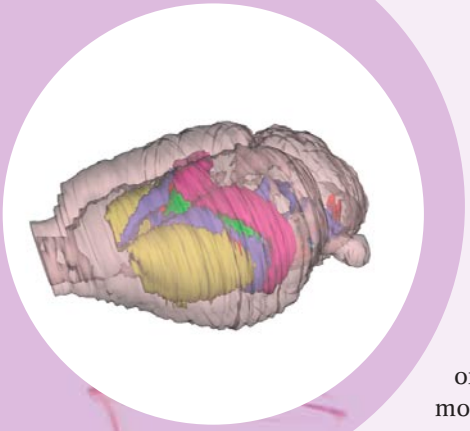
NeSys – Neural systems and graphics Computing Laboratory



3-D digital rat brain model reconstructed from a standard stereotaxic atlas, serving as localization matrix in new database facilities

About

NeSys is a computational neuroanatomy and neuroinformatics laboratory. The research of the group focuses on 1) the development of new and powerful methods for computerized data acquisition, 3-D reconstruction, visualization and quantitative analyses of features in brain tissues, 2) data management and construction of 3-D brain atlases of experimental data, and 3) investigations on organization and re-organization of brain systems architecture in rat and mouse models, and 4) *in vivo* imaging in the context of multi-modality brain atlasing.

Challenges

Much of the research carried out today on rodent models generates high resolution image data, allowing characterization and analysis of brain molecular distribution, gene expression, and connectivity. It is of great importance not only to record more data but also to integrate data, re-use data in novel combinations, and perform more powerful analyses. To this end, data management systems and advanced analytical tools are needed. Structure and structure-function relationships are often better understood by introducing 3-D reconstruction and advanced visualization and modelling tools.

Projects

1. *Neuroscience databases and atlasing systems*. We develop database applications for image data, from microscopy level to *in vivo* imaging data. We now host a rat and mouse brain work bench (www.rbwb.org), providing access to repositories, databases, and analytical tools, for circuit level as well as molecular distribution data.

2. *Localization in the brain.* We develop and use technologies (robotic microscopy data acquisition, computerised 3-D reconstruction, and digital atlasing) for efficiently assigning localization to neuroscience data.

3. *Brain map transformations.* We study design principles and changes in the architecture of major circuits in the brain following external and genetic manipulations.

4. *High resolution MRI and microPET*. In several project collaborations, tomographical imaging techniques are employed to characterize structural and functional relationships occurring in the brain following experimental perturbations or disease.

Recent achievements

1.) Development and sharing of software for 3-D reconstruction, visualization, and analysis of neuronal distribution and brain regional organization (www.rodentbrainworkbench.org). **2.)** Development of a novel digital atlas system for evaluation of cellular distribution patterns in large series of high-resolution mosaic images of histological sections (Boy et al., NeuroImage 2006; 33: 449-462, www.rodentbrainworkbench.org). **3.)** Mapping of topographical organization in cerebro-cerebellar pathways from somatosensory cortex through the pontine nuclei to different locations in the cerebellum (Odeh et al., J Neurosci. 2005; 25: 5680-5690; Leergaard et al., Eur J Neurosci. 2006; 24: 28012812). **4.)** Establishment of the first database on Functional Anatomy of the Cerebro-Cerebellar System in rat (Bjaalie et al., Neuroscience 2005; 136:681-696; Moene et al., Neuroinformatics 2007, In Press; www.rodentbrainworkbench.org).

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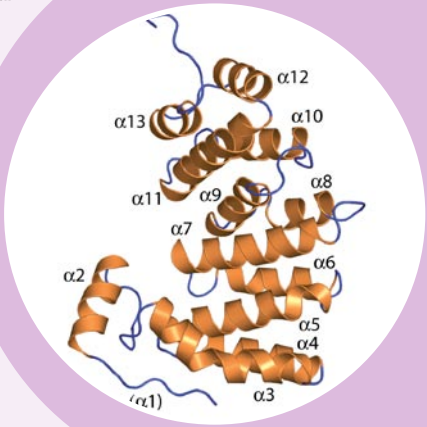
The Bioinformatics Group

About

The Bioinformatics group uses computational methods to analyse genome sequences, amino acid sequences, and gene expression data, both to identify new genes of interest and to determine their function and role in the cell. Advanced statistical and computational tools are both being used and developed. The group is also creating databases and web sites with our tools and generated data. We are involved in many collaborative projects with different research groups.



Model of the 3-dimensional structure of the AlkD enzyme, a member of a new superfamily of DNA glycosylases

Challenges

Huge amounts of molecular biology data is being generated from a range of different technologies. Complete genome sequences from hundreds and soon thousands of organisms are available. Data from many large-scale nucleic acid hybridization experiments, DNA polymorphism studies, molecular interaction experiments and protein structure determination projects is also publicly available. Apparently all this data should enable the extraction of much biological insight, but the main challenge in computational biology is to integrate and make sense of all the data. Computational analyses may be hard, but can be very powerful in many types of studies, saving a lot of work in the wet lab or permitting otherwise impossible studies.

Projects

- **Sequence similarity:** Tools like PARALIGN for particularly rapid and sensitive sequence database similarity searches have been developed. Parallel computing technology is exploited to get the highest performance. These tools are now being used to build gene homology networks and to cluster orthologous genes into groups.

- **Comparative genomics and DNA repair:** General sequence analysis and computational identification of new DNA repair genes is carried out in close collaboration with other groups. Both advanced homology based methods and comparative genomics methods are used. A web portal is being established with an underlying database containing information on DNA repair genes across species.

- **Structural bioinformatics:** Computational models of the 3D structure of proteins are created and studied in order to understand the molecular mechanisms of enzyme activities. Docking and molecular dynamics simulations are also used in our studies. Recently, we have started studies of the consistency of the structural conformation of very short segments of proteins.

- **Non-coding RNA genes:** The group is developing computational methods to identify new non-coding RNA genes (ncRNA), which are generally poorly annotated. The tool RNAmmer, based on hidden Markov models, is being developed to accurately locate ribosomal RNA genes in genomic sequences. Custom genome tiling microarrays have been designed to study transcription in “intergenic” regions.

- **DNA variation:** We are studying single nucleotide polymorphisms (SNPs) in DNA repair genes and selected other proteins. Certain DNA polymorphisms may cause disorders in individuals. How and where do polymorphisms in the human genome occur? Can we predict which polymorphisms are causing problems?

Recent achievements

Created a rapid parallel implementation of the Smith-Waterman sequence alignment algorithm (Bioinformatics 2000) and developed the heuristic PARALIGN algorithm (NAR 2001). Identified skewed distribution of DNA uptake sequences in bacterial genomes (NAR 2004). Discovered a new protein superfamily that includes two novel alkylpurine DNA repair glycosylases (Mol. Microbiol. 2006), and analysed their mechanism of repair based on a structural model (NAR, in press).

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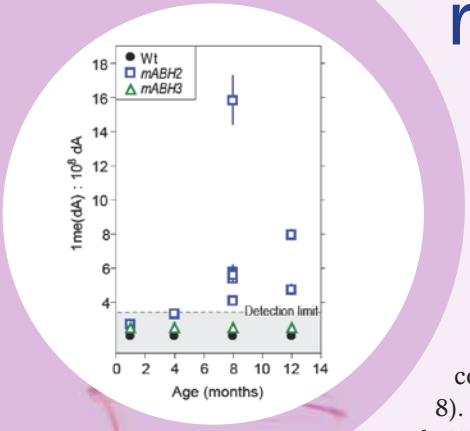
Laboratory for Genome repair and regulation



1-metyladenine (1meA) DNA base lesions accumulate in DNA repair deficient mABH2 knockout mice.

About

Erroneous methylation on the DNA molecule must be repaired. Such repair is carried out by three completely different strategies. One of these strategies was only identified very recently, oxidative demethylation, and is performed by the conserved AlkB protein. In mammals, 8 different AlkB homologs exist (ABH1-8). ABH2 has been shown to repair methylated genomic DNA *in vivo* (Ringvoll et al., EMBO j 2006). The functions of the other homologs are still unknown; roles in post translational modifications of tRNA and protein demethylation (including histone) have been proposed. Methylation is a widespread modification of DNA, RNA, and proteins. For many years such modification was considered to be irreversible, today it is established that regulated demethylation are vital for correct function of macromolecules. Numerous enzymes responsible for the introduction of methyl groups have been identified during the last two decades, but the first corresponding demethylating enzymes were identified recently. We generate gene-targeted mice lacking individual *ABH* genes in order to elucidate the in vivo role and biological roles of these homologs.

Challenges

We use standard molecular biology strategies, including the construction of cells and animals lacking specific DNA repair functions, to identify and characterize gene-functions for repair and regulation of DNA, tRNA and histones. Several collaborations, internationally and within the Centre for Molecular Biology and Neuroscience, have been initiated.

Projects

We aim to identify the role of individual genes in the ABH family for DNA repair, transcription regulation, X-chromosome inactivation and in general for post translational modifications of macromolecules.

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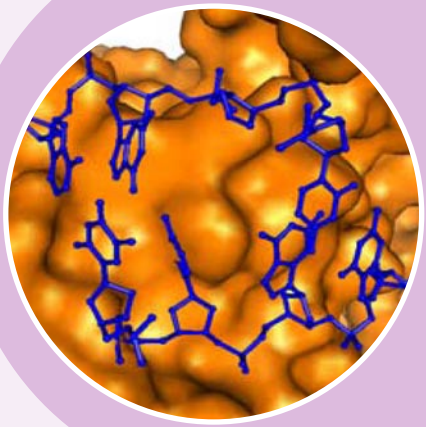
Laboratory for Molecular Biology



Mag2 bound AP DNA resembles MutS bound mismatch DNA. Superimpotion of Mag2-AP DNA on MutS surface

ABOUT

The Laboratory for Molecular Biology investigates basic biological processes associated with cellular responses to DNA damage including DNA repair pathways and mechanism for tolerance, scavenging and adaptation. Focus has been on the repair of endogenous DNA damage and mechanisms for removal of base damage to DNA. At the cellular and organismal level, the aim is to understand mechanisms for genome maintenance in mammalian as well as microbial cells and to develop new interventions for preventing cancer and neurological disease associated with genome instability caused by DNA damage.

CHALLENGES

Cellular genomes are continuously challenged by physical, chemical and biological agents that introduce changes of the chemical structure of the DNA. Intracellular reactive metabolites such as reactive oxygen species and alkylating compounds are important inducers of such changes. Nevertheless, mutation frequencies are low because of very efficient pathways for DNA repair and DNA recombination, which remove DNA damage and conserve at least one functional copy of the genome. Nevertheless, in humans, DNA damage will induce genome instability that is associated with disease and degenerative disorders. Challenges are to understand the mechanisms for cellular protection against DNA damage and its role in cancer, ageing and neurological disease.

PROJECTS

- Alkylation and oxidative DNA damage and repair - role in ageing, cancer and neurological disease
- Maintenance of mitochondrial DNA
- Functional genomics of DNA repair
- Model studies of DNA repair and ageing in yeast
- RNA genes in biological responses to DNA damage
- Mechanisms of DNA repair and genome maintenance in microbial cells and animal viruses
- Genome stability and maintenance in stem cells
- Structural biochemistry of base lesion repair

Recent achievements: Basic biology of nucleotide excision repair (Nature 263:524-6, 1976; PNAS 75:2569-73,1978; PNAS 79:988-92,1982; PNAS 87:191-4,1990; EMBO J. 3:757-60, 1994), genetics and mechanisms for repair of alkylation damage to DNA (JMB 140:101-27,1980; Nature 296:775-7,1982; EMBO J 9:4563-8,1990; EMBO J 17:363-7,1998; Nature 419:178-82,2002; Nature 421:859-63,2003), identification, cloning and characterization of genes for repair of oxidative DNA damage in eukaryotes (PNAS 93:10735-40,1996; EMBO J 16:6314-22,1997; MCB 19:3779-87,1999; NAR 30:4926-36,2002). Significant contributions have also been made in the fields of brain glutamate transport (Nature 360:464-7,1992, Eur. J. Nurosci., 6:936-42,1994), haematopoiesis (Blood 91:4127-35,1998), and bioinformatics (Bioinformatics 16:699-706,2000)

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Genome Dynamics and Microbial Pathogenesis

The meningococcal PilQ complex is a pore through which pili are extruded. J. Bacteriol. 2003

About

The stability of microbial genomes and gene pools is constantly challenged by horisontal gene transfer and recombination, as well as DNA damage. Mechanisms for rapid genome variation, adaptation and maintenance are a necessity to ensure microbial fitness and survival in rapidly changing environments. Understanding microbial pathogenesis, horizontal gene transfer, genome instability and DNA repair mechanisms requires an interdisciplinary approach of molecular biology, genomics and bacterial physiology. These studies in genetic model bacteria are most important for understanding the balance between cellular fitness for survival and disease development (Nature Microbiol. Rev. 2006). In particular, we are focusing on the identification of DNA binding components contributing to the neisserial transformation system (J. Bacteriol 2007), which we suggest is directly coupled to pilus retraction (Microbiology 2007). In this context we have identified a number of novel DNA biding components and defined how they act and interact. We are also elucidating the effect of defects in DNA repair on microbial fitness and virulence in new meningitis mouse model. At present the group addressing these challenges in molecular and cellular biology and medicine includes ten people and has strong international networks.

Challenges

To dissect how genome dynamics affect DNA sequence variability and conservation and thereby influence microbial fitness for survival and pathogenesis. Our analysis of surface structures and genome maintenance components will provide new insight into bacterial fitness and virulence. This information will enable us to develop new strategies for prevention and treatment of disease which also has relevance for eukaryotic systems.

Projects

- Meningococcal pilus biogenesis and DNA uptake: *Neisseria meningitidis* is the causative agent of meningitis. Pili are the primary virulence factor of this exclusively human pathogen. The transport of these macromolecular structures across membranes is performed by a complex machinery, which is also coupled to transformation of DNA. We are characterising the structure-function relationships and interactions of components involved in the membrane transport of pili and DNA (J Mol Biol 2006; J Structural Biol 2006; Microbiology 2007).

- Genomics in the search for novel signature DNA sequences: We are using our combined expertise on evolutionary phylogeny, prokaryote cell physiology and comparative genomics to identify new signature sequences and have defined the DNA uptake sequence as a12-mer (J. Bacteriol. 2007).

- Effects of the meningococcus on brain water homeostasis: By using cellular and animal models the effect of meningococci on glial aquaporins and other glial and neuronal components are characterized (Neuroscience 2007).

- Intracellular survival of *Mycobacterium tuberculosis*: We are studying the mechanisms for genome maintenance and thereby fitness for survival in the world's biggest bacterial killer.

Recent achievements: Secretin PilQ interactions with DNA (Microbiology 2007), antimutator role of meningococcal MutY and MutS (Nature Micro. Rev. 2006), the true identity of the neisseria DNA uptake sequence (J Bacteriol 2007)

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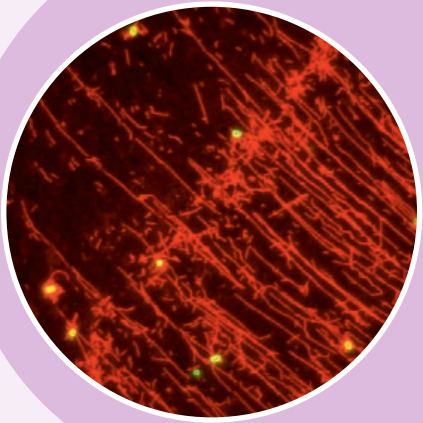
Bacterial Pathogenesis – Molecular and cell Biology

About

The main interests of the group lie in studies of how bacterial pathogens cause disease in man. Our research is focused particularly on bacterial surface organelles termed Type IV pili (Tfp) or fimbriae. Tfp expressing bacterial pathogens are responsible for an extensive amount of morbidity and mortality worldwide. Tfp expression is also associated with horizontal gene transfer and therefore contributes to the evolution of pathogenic and antibiotic resistant microbes. As such, Tfp play central roles in prokaryotic cell biology and disease pathogenesis. Moreover, retraction of single Tfp filaments generates forces in excess of 100 pN making them the most powerful biological molecular motor yet characterized. Based on both its relevance to other human diseases and its amenability to *in vitro* manipulation and analysis, we have focused on the human pathogen *Neisseria gonorrhoeae*, the agent of gonorrhea, as a model system. Exploiting advances made recently in this system, we have now expanded our studies to encompass Tfp systems in *Neisseria meningitidis* (the etiologic agent of epidemic meningitis), *Pseudomonas aeruginosa* and pathogenic species of *Francisella*.



N. gonorrhoeae expressing type IV pili from Pseudomonas aeruginosa (Immunoflourescence microscopy – cell / green, pili / red.)

Challenges

We use molecular biology strategies, together with classical genetic, genomic and proteomic approaches to elucidate the mechanisms of Tfp biogenesis and the structure/function relationships accounting for Tfp associated phenotypes. The intention is that by understanding the molecular basis for these processes, it will be possible to design rational approaches to preventing and controlling disease. Several international collaborations are ongoing.

Projects

Tfp biogenesis and dynamics of expression: As dynamic filamentous polymers, Tfp undergo rounds of extension and retraction modeled as pilin subunit polymerization and depolymerization events. Thru bioinformatics and genetic analyses we have identified a number of proteins whose absence leads to dramatically reduced levels of Tfp expression and that these defects are suppressed in the absence of the PilT pilus retraction protein. Thus, these molecules are not canonical biogenesis factors, but rather act as effectors of pilus homeostasis. Cumulatively, the observations suggest that Tfp have an exploratory character similar to that of the microtubule cytoskeleton and clathrin-based endocytic machinery. The findings have important implications for understanding Tfp dynamics and fundamental Tfp structure / function relationships. For more information please see our web page: http://www.imbv.uio.no/prot/groups/koomey/

Recent achievements: a unique pilus biogenesis pathway (EMBO J 2000); identification of two pilin-like proteins that play antagonistic roles (Mol Microbiol 2002 – 2X); down-regulation of CD46, a complement regulatory protein, by piliated *Neisseria gonorrhoeae* (JEM 2003); a force-dependent molecular switch can induce pilus elongation by reversing the retraction mechanism (PNAS 2004), discovery of posttranslational modifications of the pilin subunit (PNAS 2004); role of pilin-like molecules in Tfp dynamics and function (Mol Microbiol 2005); multisite, hierarchical protein modifications with phosphoethanolamine and phosphocholine and identification of a protein phosphoethanolamine transferase (JBC 2006) and role of a conserved pilin structural domain on Tfp assembly, dynamics and associated functions (Mol Microbiol 2006).

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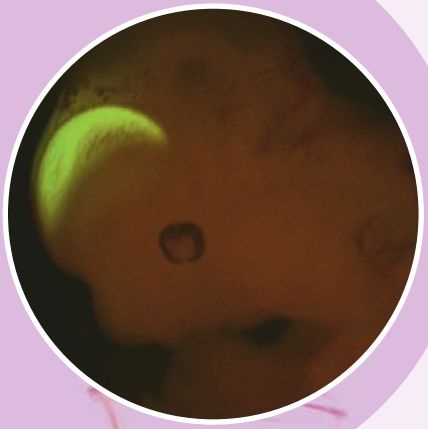
Forebrain development and Neural stem cells



The D6 enhancer allows selective genetic manipulation in the mouse cortex

About

The developmental biology laboratory investigates the signalling mechanisms that control fate specification and proliferation in the mouse cortex.

Challenges

The aim of the ongoing study is to deepen our understanding of signalling pathways that are involved in cortical development, sub-specification of cortical areas, proliferation and communication between supporting cells. Disease models will be established that shall cast light on the function of morphogenetic signals in ageing and dementia. This knowledge should help to develop new strategies for prevention and treatment of disease, either by identifying drug targets, or by developing cell based delivery of therapeutic signals.

Projects

- Understanding cortical development and evolution through cell culture and transgenic model systems.
- Study interaction and convergence of cortical signalling in animal and cell culture systems
- wnt signalling in cortical maturation and ageing

Recent achievements

Discovery of key signal Shh (Cell 1993). Mutant for manipulation of anterior inductive zone AER (Nature Genetics 1998). Cortex specific manipulation of Wnt signalling (Neuroscience 2003).

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FUNDING AND EXPENSES

The CMBN's total income of 97,5 million NOK for 2006 is 5 million NOK less then 2005, mainly as a result of a minor reduction in the Centre`s external project portfolio. The income is distributed according to the following sources of funding and expenditures:

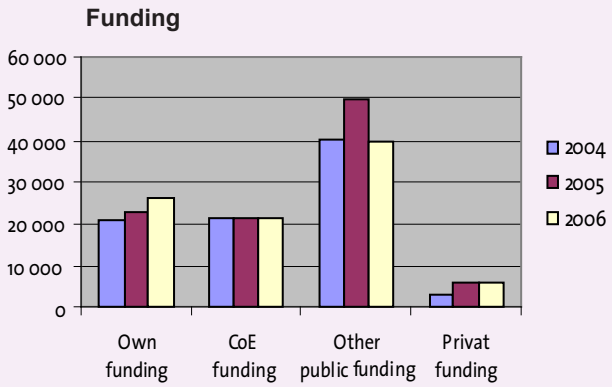
Own funding covers support from the two host institutions, The University of Oslo and RR, and includes salary, location and running costs.

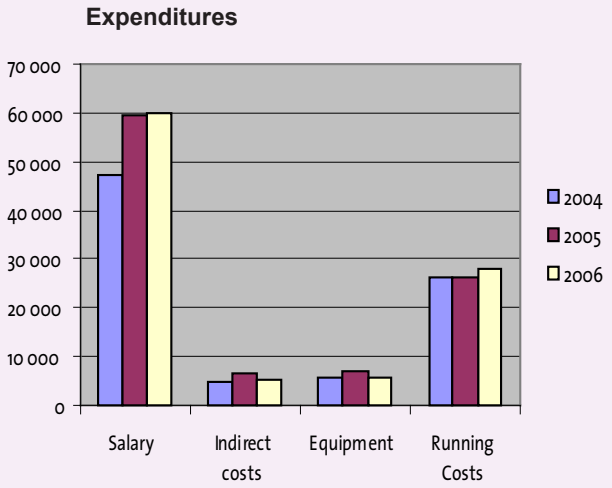
The core CoE funding is provided by the Research Council of Norway (RCN).

Other public funding/Private funding is the largest part of the CMBN financial basis and consists of over 50 different projects run by the different group leaders. The project portfolio includes three STORFORSK grants.

CMBN staff included in 2006 123,4 person years with a salary budget of 65 mill NOK. This is up 5 mill NOK from 2005.

Scientific equipment and running costs. In 2006 5,5 mill NOK was spent on equipment acquisitions and around 27 mill NOK on running costs and lab supplies.





CMBN PERSONNEL AND ASSOCIATED MEMBERS

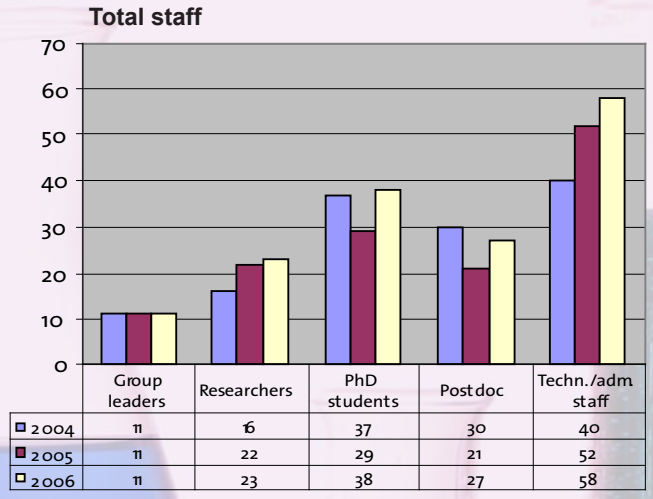
CMBN policy is to keep our doors open for new and bright people who want to take part in our research activities. In 2006 the staff counted 157 people. If we look at "person years" our statistics shows a stable work force at approximately 108 person years from 2004 to 2005 and with a small increase in 2006 to 123.4 person years. Our strategy for 2007 will be to remain the same level as 2006.

In 2006 the Centre had full time scientists from 17 different countries, including 4 senior researchers, 6 PhD students and 7 Post docs. The Technical staff included 8 foreign citizens. The proportions of men and women in the Centre are almost equal (50 %).

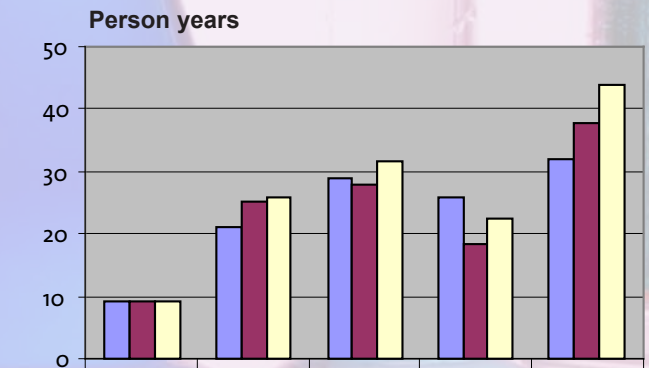
The staff/personnel was divided in different categories as shown. The increase in technical/administrative staff reflects change in budget routine.

In addition to the personnel shown in the figures, 7 "Guest researchers" and 32 master and MD students were affiliated with CMBN in 2006, including personnel funded through our Marie Curie Training Sites.

The Centre is constantly focusing on building new international networks by promoting education and mobility. We see this as an important way of recruiting the best candidates.



	Group leaders	Researchers	PhD students	Postdoc	Techn./adm staff
2004	11	16	37	30	40
2005	11	22	29	21	52
2006	11	23	38	27	58



	Group leaders	Researchers	PhD students	Post doc	Techn./adm.staff
2004	9	21	28,65	26	31,95
2005	9	25,1	27,5	18,3	37,9
2006	9	25,6	31,4	22,5	43,9

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