CENTRE FOR
MOLECULAR BIOLOGY
AND NEUROSCIENCE

ANNUAL REPORT 05

Centre for Molecular Biology and Neuroscience (CMBN)

Norwegian Centre of Excellence

UNIVERSITY OF OSLO

Rikshospitalet – Radiumhospitalet HF

SUMMARY

2005 was a very active year for The Centre for Molecular Biology and Neuroscience. Several international meetings were arranged, new networks and collaborative links were established, and much emphasis was placed on postgraduate teaching and method development. Most importantly, last year saw a high publication activity that has brought us a long way towards the ambitious goals set out in our work programme. As will be described in more detail below, CMBN researchers have published over 50 original articles in 2005. About half of these appeared in "high impact journals", here defined as journals with an ISI impact factor >6. The Centre is on schedule in regard to its research plan and is now in the process of working out the strategy for the second half of the Centre's lifetime. This strategy will build on the breakthroughs that were made during the years that have elapsed since the Centre was established in 2002.

Last year saw a reorganization of the Centre, after Erling Seeberg passed away in December 2004. Tone Tønjum was appointed Assistant Director of CMBN while Magnar Bjørås took over as Group leader after Erling. The Centre consists of 11 research groups, as at its startup in 2002, but the number of persons affiliated with the Centre has grown considerably since then and has now passed 130 (including part time positions). We have been able to recruit a large number of young and talented students and many of these are from abroad. It should be noted that the Research Curriculum at the Faculty of Medicine ("Forskerlinjen") has been instrumental in securing a good recruitment base for the Centre.

Magnar Bjørås

Tone Tønjum

In the following, we will describe in some detail the Centre's activities in 2005.

Several scientific breakthroughs were made in the course of the past year. The publication list attests to this, although many of the results will be published in 2006. Only some of the scientific results can be mentioned in the format of the present introduction.

A major breakthrough came near the end of the year, with the publication in Nature of a paper implicating NMDA receptors in the pathophysiology of white matter damage in neurodegenerative disease (Nature 438:1162-1167). This paper, coauthored by CMBN researcher Linda H Bergersen, addresses the primary goal of the Centre: to provide a better understanding of the mechanisms of cell death in the central nervous system. In the original application leading to the establishment of the Centre in 2002, this goal was formulated as follows: *The aim is within 5 years to be one of the most innovative environments internationally for the identification, development and promotion of new approaches to the treatment of brain disease and age-related neurological impairment.*

Other 2005 studies that have taken us further towards this goal is a paper published in PNAS, showing that patients with mesial temporal lobe epilepsy experience a loss of the water channel aquaporin-4 from perivascular endfeet (Proc Natl Acad Sci USA 102:1193-1198). This loss occurs in the areas of the hippocampus that exhibit neuronal loss and gliosis. Based on previous experimental observations in the Centre, a deficiency in water trans-

port through AQP4 would be expected to compromise the handling of extracellular K^+ and hence lead to an increased neuronal excitability and proneness to epileptic seizures. CMBN researchers now pursue the hypothesis that a loss of perivascular aquaporin-4 is a critical event in epileptogenesis and neuronal cell loss in mesial temporal lobe epilepsy.

Mechanisms of water transport and edema formation in the CNS have been elucidated further by two additional key papers published in 2005. The identification of carbonic anhydrase XIV in specific cell compartments in the retina (Proc Natl Acad Sci USA 102:8030-8035) may open for new strategies for the treatment of macular edema while the discovery of a short brain isoform of AQP9 (FASEB J 19:1459-1467) provides new insight in transport processes across the inner mitochondrial membrane. The latter finding may turn out to be relevant to the pathogenesis of Parkinson's disease.

One of the main visions of the Centre announced in the original application is that it shall "take on a leading role in elucidating the role of DNA repair and genome maintenance mechanisms in preventing neurological disease and brain aging". Several studies on the basic mechanisms of DNA repair have been published in the course of 2005, including a paper on repair of oxidative DNA damage in HIV infection (Blood 105:4730-4735). This paper drew a commentary in Science (see www.cmbn.no). Multiple papers on DNA repair have been published in other journals such as Oncogene and Nucleic Acids Research (see publication list). An extensive collaboration involving several CMBN groups was initiated soon after the establishment of the Centre with the specific aim of exploring the identity, expression patterns, and functional roles of the different DNA repair enzymes in the mammalian brain. This collaborative project is now in good progress and will be the focus of a Special Issue that is edited by CMBN researchers and CMBN guest professor Vilhelm Bohr. This Special Issue of the journal *Neuroscience* will be published late 2006 and will be entitled "The role of DNA repair and genome dynamics in neurological disease and aging". The same topic will be addressed in a high impact international meeting, the First Genome Dynamics in Neuroscience Meeting, organized by CMBN in April 2006 (www.cmbn.no/gdn).

Another vision of CMBN is to "develop world-class expertise within microbial pathogenesis related to human disease in general and neurological disease in particular". Work on the pathogenic Neisseria species and their surface filaments (pili) coupled to transformation of DNA is particularly relevant in this regard. In 2005, CMBN researchers identified in Neisseria a family of five proteins that are required for pilus function and that act as "gears" in the pilus motor – which is regarded as the world's strongest molecular motor (Mol Microbiol 56:903-917). This discovery may lead to new methods to control infectious diseases in the CNS and to the development of unique biological nanomotors. A review of CMBN's work on meningococcal genome dynamics highlights the unique patterns of genome instability and DNA repair in this important pathogen and model organism (Nature Microbiology Reviews, 4:1-12, 2006).

In the work program for CMBN it is stated that "the Centre will deliver diagnostic and bioinformatics tools of considerable socio-economic and potential commercial value". In 2005 the Centre has delivered on this promise by publishing a "kind of Google for genes". This is a web service (called PARALIGN) for rapid and accurate searches in genetic sequence databases (Nucleic Acids Res 33 (Suppl. 2): W535-W538). The Centre is also in the process of developing potent neuroinformatics tools (J Neurosci 25:5680-5690).

Finally, it should be mentioned that it is an aim of the Centre to "develop and apply stem cell technology and targeted repair to broaden the range of therapeutic strategies in neurological disease". Significant advances in this line of research have been made in the course of the last year (Mol Cell Neurosci 30:388-397). There has also been substantial progress in our understanding of the functional roles of K+ channels and glutamate transporters in the CNS (Nature Neurosci 8:51-60, J Neurosci 25:8482-8497).

Many of the above studies have drawn on the complementary and multidisciplinary expertise of the different CMBN groups and have capitalized on the broad range of technologies that are available within the Centre. A main philosophy of the Centre that has been duly followed up in 2005 is to use a substantial proportion of the CMBN core funding to acquire equipment and expertise that provide optimum

opportunities for state of the art studies within the fields covered by the CMBN research program. Method development is also important and 2005 saw a publication on refinement of RNA interference methodology for knocking down the expression of DNA repair enzymes and water channels (Nucleic Acids Res 33: 4704-4710, 2005). The latter study could only have been accomplished through the joint efforts of two CMBN groups.

The CMBN research program enclosed with the original application listed six different subgoals for the Centre. Five of these have been referred to above. The sixth goal was phrased as follows: "The Centre will take on a primary responsibility for postgraduate teaching in the research field at the crossroads between molecular biology, genetics and neuroscience." CMBN has been appointed as a Postgraduate School ("Forskerskole") at the University of Oslo and has invested a substantial part of its budget in advanced courses and symposia. The philosophy has been that the Centre's PhD students and postdocs shall be introduced to the international leaders in the field. This has been duly implemented in 2005 through the organization of several symposia including symposia on "Mitochondrial Function: Basic Mechanisms and Clinical Aspects" and "Transport Processes in the CNS". The full programs of these events are found on www.cmbn.no and include lectures by two Nobel Laureates within the research field of the Centre. In addition to the symposia the Centre organized 18 CMBN lectures in the course of 2005. Only top tier researchers can qualify as CMBN lecturers and these are invited on the premise that they shall contribute to the education of the PhD students of the Centre. Obviously, the PhD training is also a major responsibility of the CMBN guest professors. These are expected to spend several weeks at CMBN every year and to contribute to CMBN's symposia and other CMBN activities.

It should also be mentioned that CMBN has made significant accomplishments in 2005 in regard to the aim of building new collaborative networks devoted to the CMBN research programme. Through the influx of new expertise and financial resources, such networks will increase the likelihood of reaching the ambitious goals of the Centre. In February 2005 it was announced that three of the STORFORSK grants from the Norwegian Research Council were awarded to CMBN researchers. Further, 2005 saw the establishment of new EU projects, coordinated by CMBN researchers with the aim of expanding the range of expertise available to the Centre – for research as well as for PhD education. CMBN is also partner in a new EU sponsored network (CORTEX) that was established in 2005 with the specific goal of providing a broad and multidisciplinary training of talented PhD students.

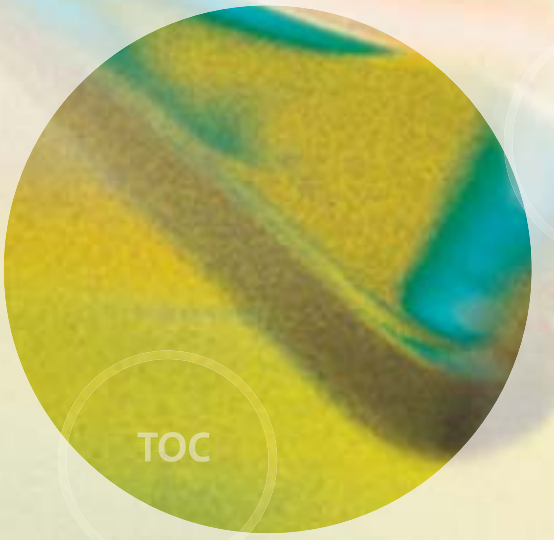
Last, but not least, it deserves emphasis that the Centre in 2005 has continued its strong emphasis on building well functioning networks between its constituent groups. CMBN has established specific groups for its PhD and postdoctoral students and has organized several practical courses to help CMBN researchers familiarize themselves with newly acquired advanced equipment and technologies. Epitomizing the growing synergies within the Centre, the CMBN established a team for Holmenkollstafetten and completed the relay in 67 minutes 56 seconds. This meant that the Centre finished in 9th place among the 77 teams in its class. Needless to say, this accomplishment was duly celebrated.

Finally, it is appropriate to thank the Norwegian Research Council and all the others who have supported the activities of the Centre in the course of 2005. In particular we would like to acknowledge the expert assistance of the administrative staffs of the Institute of Basic Medical Sciences and the Institute of Microbiology. Our thanks are also extended to our host institutions: the Faculty of Medicine and Faculty of Mathematics and Natural Sciences, University of Oslo, and Rikshospitalet-Radiumhospitalet Health Authority, which have been instrumental in securing optimal working conditions for the Centre.

Ole Petter Ottersen

Tone Tønjum

TABLE OF CONTENTS



AWARDS AND DOCTORAL DEGREES

Awards 2005

CMBN Professors Ole Petter Ottersen and Jon Storm-Mathisen were awarded the **Lundbeck Foundation Nordic Research Award 2005** of 1.5 million Danish kroner for their accomplishments in neuroscience research.

Marina Aspholm, who joined CMBN and professor Michael Koomey' s group as a postdoctoral fellow in January 2005 after having done her PhD at Umeå Univ. with Prof. Thomas Boren and who is the recipient of an EMBO longterm fellowship, was given the **Top Young Scientist Award in Europe** for molecular biology (2005) granted by GE Healthcare together with the journal *Science*.

AWARDS AND DOCTORAL DEGREES

Doctoral degrees 2005

Cand. scient. Tonje Davidsen defended her PhD dissertation with the title; "Genome instability and maintenance in Neisseria meningitidis". The candidate was supervised by CMBN group leader Tone Tønjum.

Hua Hu, MD, defended his PhD dissertation with the title; "Functions of Ca2+-activated and KCNQ/M-type potassium channels in the brain". The candidate was supervised by CMBN group leader Johan F. Storm.

Cand. Scient. Elisabeth Larsen defended her PhD dissertation with the title: "Mouse models for flap endonuclease (FEN1) and 8-oxoguanine DNA glycosylase 1 (OGG1) deficiency". The candidate was supervised by CMBN group leader Arne Klungland.

M.Sc. Christian Johannes van den Bout defended his PhD dissertation with the title: "Developing tools for manipulating gene expression in the cortex and hippocampus". The candidate was supervised by CMBN group leader Stefan Krauss.

Cand. real. Juris Allunans defended his PhD dissertation with the title; "Bacteriocinogeny in Neisseria meningitidis isolates associated with the epidemic starting in North Norway in the mid-1970's". The candidate was supervised by Kaare Jyssum, Kjell Bøvre and Erling Seeberg.

NETWORKS

Gaustad Neuroscience Network (GNN) was established at the initiative of CMBN. This network aims to link basic science and clinical research at Gaustad and addresses all aspects of neuroscience represented on the campus. The goal is to heighten the awareness of activities, competence and resources available locally, to elicit new collaborations, and increase the output from ongoing research. The ambition is that GNN should develop into a multidisciplinary neuroscience research environment at the highest international level. New funding will have to be generated for GNN research activities.

GNN was formally established on January 21, 2005, but had a preliminary kick-off already in October 2004 at the joint CMBN - GNN event Forskerkurs IV: "Recent advances in molecular biology and neuroscience". Each topic at this course was addressed jointly by a basic and clinical neuroscientist. CMBN contributes to GNN by 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 2005 included participation at the NCoE / WIRED meeting in June 2005.

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.

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)** 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 **(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.

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") concept established by the University of Oslo in 2004. CMBN Research school is lead by group leader Tone Tønjum. The following seminars were held in 2005:

First Norwegian Transgenic Animal Forum at Lysebu, Oslo, 10-11 February 2005
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.

Synaptic homeostasis and brain disease, 18 March 2005.
The open, international symposium was held at the 50th anniversary of Centre Director Ole Petter Ottersen. Fifteen speakers from seven countries (Finland, France, Japan, Norway, Sweden, UK, USA) discussed this theme which is an important focus of CMBN research.

CMBN research seminar on mitochondrial function, 14-15 April 2005
CMBN research seminar (forskerkurs) in Store Auditorium, Rikshospitalet. The objective of the course was to highlight various aspects of mitochondrial function and to emphasize the central role that mitochondrial dysfunction plays in many diseases. Mitochondrial dysfunction is characteristic of several neurological diseases, cancer, life style diseases as well as aging in general. Topics presented covered mitochondrial homeostasis, including mitochondrial DNA replication and repair, oxidative stress, calcium signaling and energy metabolism. Seminar contributors included internationally leading scientists in the field of mitochondrial science.

Bioinformatics for young scientists (BFYS2005) at Randsvangen, 15-17 April 2005
BFYS2005 brought together young bioinformatics scientists working in Norwegian institutions and companies. The meeting was held at Randsvangen Hotel, at Jevnaker, starting with lunch Friday April 15, and ending with a late lunch Sunday April 17. The meeting was organized by the Bioinformatics Group at the CMBN.

WIRED-symposium – Nordic Centre of Excellence, 18-24 May 2005
This symposium was organized jointly with CMBN and GNN and was the kickoff meeting of the newly established Nordic Centre of Excellence for Research in Water Imbalance Related Disorders (WIRED).

MedCoast Symposium, 4 November 2005 – The CMBN was a major scientific contributor
The Symposium was arranged as part of the ScanBalt Forum 2005. A major scientific event was the plenary symposium in Neuroscience and Metabolic Disorders. This unique meeting had world leading scientists, including two Nobel Laureates, Arvid Carlsson and Peter Agre (CMBN guest professor). CMBN researchers gave presentations of the latest findings in molecular biology.

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

CMBN PhD group activities 2005

The PhD student group meets 2-3 times each semester to discuss science and to inform about the PhD programme and new acquisitions of equipment and technologies at the 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. Since the group was established, it has had meetings in all of the CMBN departments.

In 2005 the group had a meeting in "The synaptic neurochemistry laboratory", where Farrukh A Chaudhry gave an introduction to the anatomy of the brain, including a visit in the dissection room. In the second scientific meeting of the year the group was invited to "The bioinformatics group", where Jon K Lærdahl talked on how he experienced his years as a PhD student. The scientific meetings in the PhD group are followed by refreshments and discussion. In addition to participating in the PhD group meetings, the PhD students take part in CMBN lectures and courses.

One of the social activities in 2005 was an excellent skiing trip to Oppdal. Some of the PhD group members contributed to CMBN's success in Holmekollstafetten.

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 2005 the following four CMBN "Guest Professors" were formally appointed:

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

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.

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

Additional visiting researchers affiliated within the Centre;
Hans Krokan, Professor at the Institute of Cancer Research and Molecular Biology, NTNU, Trondheim.

Karl Peter Giese, Professor in the Department of Anatomy, University College London

Peter Agre, Professor and Nobel Prize winner in Chemistry, 2003, Johns Hopkins University, Baltimore, USA, now moved to Duke University.

Shankar Subramaniam, Professor of Bioengineering, Chemistry and Biochemistry at the University of California at San Diego, and Senior Fellow at the San Diego Supercomputer Center.

Stephen H. Koslow, Associate Director, NIMH, NIH, Bethesda, and Director of the Office of Neuroinformatics.

Jeremy Derrick and Richard Collins, Department of Biomolecular Sciences, University of Manchester, UK

Simon Kroll and Sunita Sinha, Molecular Infectious Diseases Group, Department of Paediatrics, Faculty of Medicine, Imperial College, London.

Thomas Nyström, Department of Cell and Molecular Biology, Gothenborg University.

CMBN seminars/guest lecturers

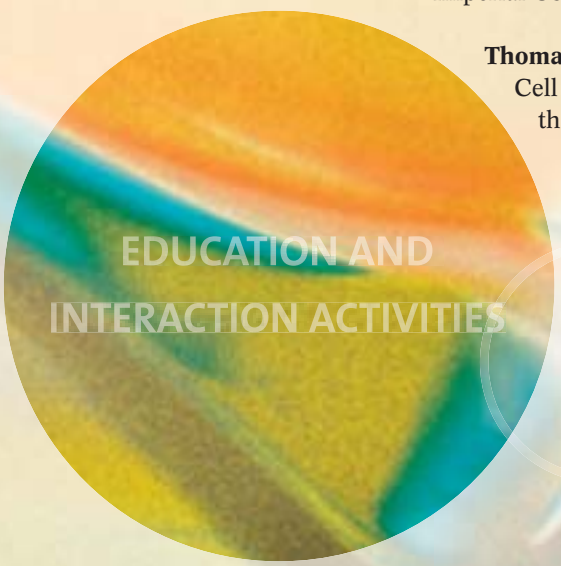
Altogether, 18 CMBN seminars were held in 2005 with high-profile researchers from abroad as specially invited lecturers. These guest lectures were arranged on the initiative of the Centre management or group leaders. CMBN seminars are open to all and are widely announced.

The Centre's lecture series for 2005 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 in 2005 postponed to February 2006 and 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.



EDUCATION AND INTERACTION ACTIVITIES

COLLABORATING PARTNERS

CMBN has over 40 ongoing co-operative relationships with research communities in numerous countries, of which 26 were in Europe and 14 in the USA and others in Australia and Japan. Among these are recognised international research institutes such as:

Anders Dale, Department of Radiology, Harvard Medical Schoo ***l***, USA
Matthias A. Hediger, Harvard Medical School, USA
Dennis D. Spencer, Yale University, USA
Tore Eid, Department of Neurosurgery, School of Medicine, Yale University, USA
Nihal C de Lanerolle, School of Medicine, Yale University, USA
Peter Agre, Johns Hopkins Medical School, USA
Stanley Froehner, Department of Physiology and Biophysics, University of Washington, Seattle, USA
Xavier Nassif, Institut Pasteur, France
Bert Sakmann, Department of Cell Physiology, Max-Planck-Institute, Heidelberg, Germany
Peter Seeburg, Department of Molecular Neurobiology, Max-Planck-Institute, Heidelberg, Germany
Vilhelm A. Bohr, Laboratory of Molecular Gerontology, National Institutes of Health, Baltimore, USA
John A. Tainer, The Scripps Research Institute, California, USA
Robert H. Edwards, University of California, San Francisco, USA
John Rubenstein, University of California, San Francisco, USA
Jeremy Henley, University of Bristol, UK
David Atwell, University College London, UK
Dimitri M. Kullmann, Institute of neurology, University College, London, UK
Søren Brunak, Center for Biological Sequence Analysis (CBS), Technical University of Denmark (DTU), Denmark
Anders Gorm Pedersen, Center for Biological Sequence Analysis (CBS), Technical University of Denmark (DTU), Denmark
Jeremy Derrick, The University of Manchester, UK
Anne Dell, Imperial College London, UK
Simon Kroll, Imperial College London, UK
Olaf Pongs, Universität Hamburg, Germany
Dirk Isbrandt, Universität Hamburg, Germany
Peter Ruth, Universität Tübingen, Germany
Karl-Peter Giese, University College London, UK
Lyle J. Graham, CNRS, Université René Descartes, Paris, France
Jean Marc Egly, Institut de Genetique et de Biologie Moléculaire et Cellulaire, GBMC, Strasbourg, France
Cynthia McMurray, Mayo Clinic, Rochester, USA
Piet Borst, The Netherlands Cancer Institute, NCI, Amsterdam, Holland
Berenike Maier, Institut für Allgemeine Zoologie und Genetik, Westfälische Wilhelms Universität, Münster
Erwin Frey, Department of Statistical and Biological Physics, LMU München
Thomas Duke, Department of Physics, University of Cambridge, UK
Åke Forseberg, Department of Medical Countermeasures, Division of NBC Defense, Swedish Defense Research Agency, Umeå
Jos van Putten, Department of Infectious Diseases and Immunology, Utrecht University
Barbara Imperiali, Department of Chemistry, MIT, Boston
Thomas Nystrøm, Department of Cell and Molecular Biology, Göteborg University
Anne Dell, Division of Molecular Biosciences, Imperial College, London
Andrea Volterra, Insitut de Biologie Cellulaire et de Morphologie (IBCM), Univesité de Lausanne

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)

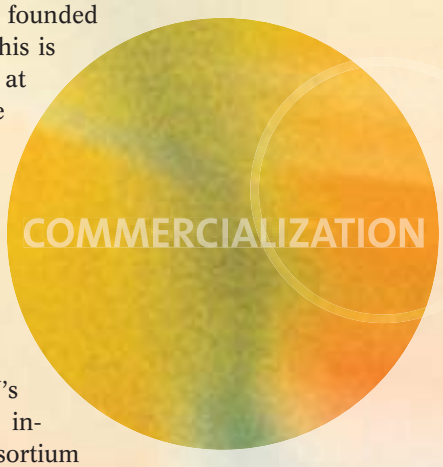
SiRNASENSE A/S founded in December 2004. This is a company that aims at developing Anti-sense Therapeutics, RNA/ SiRNA for pharmaceutical therapeutics.

As part of our commercialization strategy two of CMBN's research groups are involved in each consortium applying for status as Centre for Research Driven Innovation initiated by the Research Council of Norway.

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.



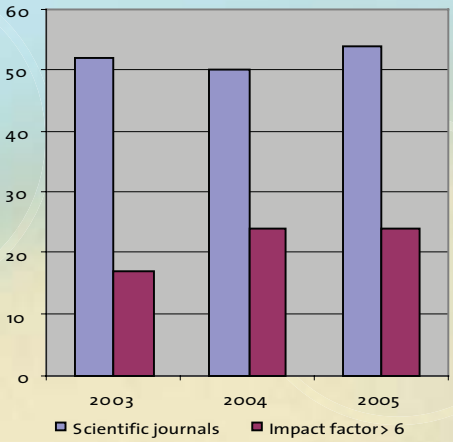
PUBLICATIONS

JANUARY 05 – DECEMBER 05

Abstracts not included

High impact papers (impact factor >6.0, according to ISI 2002) are indicated by *

1. *Alseth I, Osman F, Korvald H, Tsaneva I, Whitby MC, Seeberg E, Bjoras M (2005) Biochemical characterization and DNA repair pathway interactions of Mag1-mediated base excision repair in Schizosaccharomyces pombe. Nucleic Acids Res 33:1123-1131. (Impact 7,1)
2. *Amiry-Moghaddam M, Lindland H, Zelenin S, Roberg BA, Gundersen BB, Petersen P, Rinvik E, Torgner IA, Ottersen OP (2005) Brain mitochondria contain aquaporin water channels: evidence for the expression of a short AQP9 isoform in the inner mitochondrial membrane. FASEB J 19:1459-1467. (Impact 7,3)
3. *Aukrust P, Luna L, Ueland T, Johansen RF, Muller F, Froland SS, Seeberg EC, Bjoras M (2005) Impaired base excision repair and accumulation of oxidative base lesions in CD4+ T cells of HIV-infected patients. Blood 105:4730-4735. (Impact 9,2)
4. Backman M, Machon O, Mygland L, van den Bout CJ, Zhong W, Taketo MM, Krauss S (2005) Effects of canonical Wnt signaling on dorso-ventral specification of the mouse telencephalon. Dev Biol 279:155-168.
5. Berg BG, Almaas TJ, Bjaalie JG, Mustaparta H (2005) Projections of male-specific receptor neurons in the antennal lobe of the Oriental tobacco budworm moth, Helicoverpa assulta: a unique glomerular organization among related species. J Comp Neurol 486:209-220.
6. *Bergersen LH, Magistretti PJ, Pellerin L (2005) Selective postsynaptic co-localization of MCT2 with AMPA receptor GluR2/3 subunits at excitatory synapses exhibiting AMPA receptor trafficking. Cereb Cortex 15:361-370. (Impact 6,6)
7. Bernard-Trifilo JA, Kramar EA, Torp R, Lin CY, Pineda EA, Lynch G, Gall CM (2005) Integrin signaling cascades are operational in adult hippocampal synapses and modulate NMDA receptor physiology. J Neurochem 93:834-849.
8. Bjaalie JG, Leergaard TB, Lillehaug S, Odeh F, Moene IA, Kjode JO, Darin D (2005) Database and tools for analysis of topographic organization and map transformations in major projection systems of the brain. Neuroscience 136:681-695.
9. Bjaalie JG, Leergaard TB Three-dimensional visualization and analysis of wiring patterns in the brain: experiments, tools, models, and databases. In: 'Databasing the brain: From data to knowledge' (eds. SH Koslow and S Subramaniam). 2005; pp. 349-368. John Wiley & Sons.
10. Boulland JL, Levy LM. (2005) Glutamate, glutamine and ischaemia in the central nervous system. Tidsskr Nor Laegeforen Jun 2;125(11):1479-81. Review. Norwegian.
11. *Collins RF, Frye SA, Balasingham S, Ford RC, Tonjum T, Derrick JP (2005) Interaction with type IV pili induces structural changes in the bacterial outer membrane secretin PilQ. J Biol Chem 280:18923-18930. (Impact 6,4)
12. Davidsen T, Bjoras M, Seeberg EC, Tonjum T (2005) Antimutator role of DNA glycosylase MutY in pathogenic Neisseria species. J Bacteriol 187:2801-2809.
13. *Eid T, Lee TS, Thomas MJ, Amiry-Moghaddam M, Bjornsen LP, Spencer DD, Agre P, Ottersen OP, de Lanerolle NC (2005) Loss of perivascular aquaporin 4 may underlie deficient water and K+ homeostasis in the human epileptogenic hippocampus. Proc Natl Acad Sci U S A 102:1193-1198. (Impact 10,2)
14. Eide L, McMurray CT (2005) Culture of adult mouse neurons. Biotechniques 38:99-104.
15. *Gill DB, Spitzer D, Koomey M, Heuser JE, Atkinson JP (2005) Release of host-derived membrane vesicles following pilus-mediated adhesion of Neisseria gonorrhoeae. Cell Microbiol 7:1672-1683. (Impact 6,1)
16. Gu N, Vervaeke K, Hu H, Storm JF (2005) Kv7/KCNQ/M and HCN/h, but not KCa2/SK channels, contribute to the somatic medium after-hyperpolarization and excitability control in CA1 hippocampal pyramidal cells. J Physiol 566:689-715.
17. Hagen-Larsen H, Laerdahl JK, Panitz F, Adzhubei A, Hoyheim B (2005) An EST-based approach for identifying genes expressed in the intestine and gills of presmolt Atlantic salmon (Salmo salar). BMC Genomics 6:171.
18. Hedlund BP, Tønjum T (2005) Genus Simonsiella. In Garrity, G.M. (ed Bergey's Manual of Systematic Bacteriology Volume 2: The Proteobacteria, Garrity, 2nd ed., 2005, Springer Verlag New York, Inc., ISBN: 0-387-24145-0, pp. 844-851.
19. *Holen T, Moe SE, Sorbo JG, Meza TJ, Ottersen OP, Klungland A (2005) Tolerated wobble mutations in siRNAs decrease specificity, but can enhance activity in vivo. Nucleic Acids Res 33:4704-4710. (Impact 7,1)
20. Holmseth S, Dehnes Y, Bjornsen LP, Boulland JL, Furness DN, Bergles D, Danbolt NC (2005) Specificity of antibodies: unexpected cross-reactivity of antibodies directed against the excitatory amino acid transporter 3 (EAAT3). Neuroscience 136:649-660.
21. *Káradóttir R, Cavelier P, Bergersen LH, Attwell D (2005) NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. Nature 438:1162-1166. (Impact 32,2) Editorial comments: Nature, Editor's Summary; http://www.nature.com/nature/journal/v438/n7071/edsumm/e051222-14.html Science STKE, Vol. 2006, Issue 316, pp. tw461, 3 January 2006; http://stke.sciencemag.org/cgi/content/abstract/sigtrans;2006/316/tw461
22. *Larsen E, Reite K, Nesse G, Gran C, Seeberg E, Klungland A (2005) Repair and mutagenesis at oxidized DNA lesions in the developing brain of wild-type and Ogg1(-/-) mice. Oncogene. (Impact 6,7)
23. Lorico A, Bratbak D, Meyer J, Kunke D, Krauss S, Plott WE, Solodushko V, Baum C, Fodstad O, Rappa G (2005) Gamma-glutamylcysteine synthetase and L-buthionine-(S,R)-sulfoximine: a new selection strategy for gene-transduced neural and hematopoietic stem/progenitor cells. Hum Gene Ther 16:711-724.
24. *Luna L, Rolseth V, Hildrestrand GA, Otterlei M, Dantzer F, Bjoras M, Seeberg E (2005) Dynamic relocalization of hOGG1 during the cell cycle is disrupted in cells harbouring the hOGG1-Cys326 polymorphic variant. Nucleic Acids Res 33:1813-1824. (Impact 7,1)
25. Machon O, Backman M, Krauss S, Kozmik Z (2005) The cellular fate of cortical progenitors is not maintained in neurosphere cultures. Mol Cell Neurosci 30:388-397.
26. Malmierca MS, Bjaalie JG, Mugnaini E (2005) Theodor W. Blackstad (1925-2003): a pioneer in quantitative neuroanatomy. Neuroscience 136:601-606.
27. Morland I, Luna L, Gustad E, Seeberg E, Bjoras M (2005) Product inhibition and magnesium modulate the dual reaction mode of hOgg1. DNA Repair (Amst) 4:381-387.
28. *Nagelhus EA, Mathiisen TM, Bateman AC, Haug FM, Ottersen OP, Grubb JH, Waheed A, Sly WS (2005) Carbonic anhydrase XIV is enriched in specific membrane domains of retinal pigment epithelium, Muller cells, and astrocytes. Proc Natl Acad Sci U S A 102:8030-8035. (Impact 10,2)
29. Nase G, Helm PJ, Reppen T, Ottersen OP (2005) A multi photon laser scanning microscope setup for trans-cranial in vivo brain imaging on mice. Rev of Scientific Instruments 76:123702-1 - 123702-5.
30. *Odeh F, Ackerley R, Bjaalie JG, Apps R (2005) Pontine maps linking somatosensory and cerebellar cortices are in register with climbing fiber somatotopy. J Neurosci 25:5680-5690. (Impact 8,3)
31. Olsen PA, Randol M, Krauss S (2005) Implications of cell cycle progression on functional sequence correction by short single-stranded DNA oligonucleotides. Gene Ther 12:546-551.
32. Olsen PA, Randol M, Luna L, Brown T, Krauss S (2005) Genomic sequence correction by single-stranded DNA oligonucleotides: role of DNA synthesis and chemical modifications of the oligonucleotide ends. J Gene Med 7:1534-1544.
33. Ottersen OP (2005) Time for a more intensive Swedish-Norwegian research cooperation. Tidsskr Nor Laegeforen 125:1513-1515.
34. *Ottersen OP (2005) Neurobiology: sculpted by competition. Nature 434:969. (Impact 32,2)
35. Owe SG, Bogen IL, Walaas SI, Storm-Mathisen J, Bergersen LH (2005) Ultrastructural quantification of glutamate receptors at excitatory synapses in hippocampus of synapsin I+II double knock-out mice. Neuroscience 136:769-777.
36. Pellerin L, Bergersen LH, Halestrap AP, Pierre K (2005) Cellular and subcellular distribution of monocarboxylate transporters in cultured brain cells and in the adult brain. J Neurosci Res 79:55-64.
37. *Peters HC, Hu H, Pongs O, Storm JF, Isbrandt D (2005) Conditional transgenic suppression of M channels in mouse brain reveals functions in neuronal excitability, resonance and behavior. Nat Neurosci 8:51-60. (Impact 17,0)
38. *Renden R, Taschenberger H, Puente N, Rusakov DA, Duvoisin R, Wang LY, Lehre KP, von Gersdorff H (2005) Glutamate transporter studies reveal the pruning of metabotropic glutamate receptors and absence of AMPA receptor desensitization at mature calyx of held synapses. J Neurosci 25:8482-8497. (Impact 8,3)



39. Rozalski R, Siomek A, Gackowski D, Foksinski M, Gran C, Klungland A, Olinski R (2005) Substantial decrease of urinary 8-oxo-7,8-dihydroguanine, a product of the base excision repair pathway, in DNA glycosylase defective mice. Int J Biochem Cell Biol 37:1331-1336.

40. *Ruiz A, Sachidhanandam S, Utvik JK, Coussen F, Mulle C (2005) Distinct subunits in heteromeric kainate receptors mediate ionotropic and metabotropic function at hippocampal mossy fiber synapses. J Neurosci 25:11710-11718. (Impact 8,3)

41. Runden-Pran E, Tanso R, Haug FM, Ottersen OP, Ring A (2005) Neuroprotective effects of inhibiting N-methyl-D-aspartate receptors, P2X receptors and the mitogen-activated protein kinase cascade: a quantitative analysis in organotypical hippocampal slice cultures subjected to oxygen and glucose deprivation. Neuroscience 136:795-810.

42. *Rusakov DA, Saitow F, Lehre KP, Konishi S (2005) Modulation of presynaptic Ca2+ entry by AMPA receptors at individual GABAergic synapses in the cerebellum. J Neurosci 25:4930-4940. (Impact 8,3)

43. Sausbier M, Arntz C, Bucurenciu I, Zhao H, Zhou XB, Sausbier U, Feil S, Kamm S, Essin K, Sailer CA, Abdullah U, Krippeit-Drews P, Feil R, Hofmann F, Knaus HG, Kenyon C, Shipston MJ, Storm JF, Neuhuber W, Korth M, Schubert R, Gollasch M, Ruth P. (2005) Elevated blood pressure linked to primary hyperaldosteronism and impaired vasodilation in BK channel-deficient mice. Circulation 112:60-68. (Impact 9,9)

44. Shigenaga Y, Moritani M, Oh SJ, Park KP, Paik SK, Bae JY, Kim HN, Ma SK, Park CW, Yoshida A, Ottersen OP, Bae YC (2005) The distribution of inhibitory and excitatory synapses on single, reconstructed jaw-opening motoneurons in the cat. Neuroscience 133:507-518.

45. Shin EJ, Suh SK, Lim YK, Jhoo WK, Hjelle OP, Ottersen OP, Shin CY, Ko KH, Kim WK, Kim DS, Chun W, Ali S, Kim HC (2005) Ascorbate attenuates trimethyltin-induced oxidative burden and neuronal degeneration in the rat hippocampus by maintaining glutathione homeostasis. Neuroscience 133:715-727.

46. *Solbu TT, Boulland JL, Zahid W, Lyamouri Bredahl MK, Amiry-Moghaddam M, Storm-Mathisen J, Roberg BA, Chaudhry FA (2005) Induction and targeting of the glutamine transporter SN1 to the basolateral membranes of cortical kidney tubule cells during chronic metabolic acidosis suggest a role in pH regulation. J Am Soc Nephrol 16:869-877. (Impact 6,3)

47. *Sæbø PE, Andersen SM, Myrseth J, Laerdahl JK, Rognes T (2005) PARALIGN: rapid and sensitive sequence similarity searches powered by parallel computing technology. Nucleic Acids Res 33:W535-W539. (Impact 7,1)

48. *Sætrom P, Sneve R, Kristiansen KI, Snove O, Jr., Grunfeld T, Rognes T, Seeberg E (2005) Predicting non-coding RNA genes in Escherichia coli with boosted genetic programming. Nucleic Acids Res 33:3263-3270. (Impact 7,1)

49. Tønjum,T. (2005) Order Neisseriales. In Garrity, G.M. (ed.) Bergey's Manual of Systematic Bacteriology Volume 2: The Proteobacteria, Garrity, George M. (Ed.) 2nd ed., 2005, Springer Verlag New York, Inc., ISBN: 0-387-24145-0, p. 774.

50. Tønjum,T. (2005) Family Neisseriaceae. In Garrity, G.M. (ed Bergey's Manual of Systematic Bacteriology Volume 2: The Proteobacteria, Garrity, 2nd ed., 2005, Springer Verlag New York, Inc., ISBN: 0-387-24145-0, pp. 775-776.

51. Tønjum,T. (2005) Genus Neisseria. In Garrity, G.M. (ed Bergey's Manual of Systematic Bacteriology Volume 2: The Proteobacteria, Garrity, 2nd ed., 2005, Springer Verlag New York, Inc., ISBN: 0-387-24145-0, pp. 777-798.

52. Tønjum,T. (2005) Genus Alysiella In Garrity, G.M. (ed Bergey's Manual of Systematic Bacteriology Volume 2: The Proteobacteria, Garrity, 2nd ed., 2005, Springer Verlag New York, Inc., ISBN: 0-387-24145-0, pp. 798-801.

53. *Winther-Larsen HC, Wolfgang M, Dunham S, van Putten JP, Dorward D, Lovold C, Aas FE, Koomey M (2005) A conserved set of pilin-like molecules controls type IV pilus dynamics and organelle-associated functions in Neisseria gonorrhoeae. Mol Microbiol 56:903-917. (Impact factor 6.0)

54. Zaborszky L, Buhl DL, Pobalashingham S, Bjaalie JG, Nadasdy Z. (2005) Three-dimensional chemoarchitecture of the basal forebrain: spatially specific association of cholinergic and calcium binding protein-containing neurons. Neuroscience 136:697-713.

55. *Zhang L, Shimoji M, Thomas B, Moore DJ, Yu SW, Marupudi NI, Torp R, Torgner IA, Ottersen OP, Dawson TM, Dawson VL. (2005) Mitochondrial localization of the Parkinson's disease related protein DJ-1: implications for pathogenesis. Hum Mol Genet 14:2063-2073. (Impact 7,8)

2006:

1. Adzhubei AA, Laerdahl JK, Vlasova AV. (2006) preAssemble: a tool for automatic sequencer trace data processing BMC Bioinformatics, 2006, 7, 22.

2. Alseth I, Rognes T, Lindbäck T, Solberg I, Robertsen K, Kristiansen KI, Mainieri D, Lillehagen L, Kolstø AB, Bjørås M. (2006) A new protein superfamily includes two novel 3-methyladenine DNA glycosylases from Bacillus cereus, AlkC and AlkD Molecular Microbiology. (in press)

3. Bergersen LH, Thomas M, Johannsson E, Waerhaug O, Halestrap A, Andersen K, Sejersted OM, Ottersen OP. (2006) Cross-reinnervation changes the expression patterns of the monocarboxylate transporters 1 and 4: an experimental study in slow and fast rat skeletal muscle. Neuroscience in press. [Epub 2006 Jan 27]

4. Bogen IL, Boulland JL, Mariussen E, Wright MS, Fonnum F, Kao HT, Walaas SI. (2006) Absence of synapsin I and II is accompanied by decreases in vesicular transport of specific neurotransmitters. J Neurochem Mar;96(5):1458-66. PMID: 16478532. [PubMed - in process]

5. Davidsen T, Ambur OH, Tønjum T. (2006) Transformation and DNA repair. In: Frosch, M. & Maiden, M. In: Handbook of meningococci, WILEY-VCH Verlag Bonn Inc., ISBN 3-527-31260-9.

6. *Davidsen T, Tønjum T. (2006) Meningococcal genome dynamics Nature Microbiology Reviews 4 (1): 1-12, 2006. (Impact 9,4)

7. Klungland A, Laerdahl JK, Rognes T. (2006) OGG1: from structural analysis to the knockout mouse. Oxidative Damage to Nucleic Acids. (Eds. Evans and Cooke) (in press)

8. Martín-Ibanez R, Jenstad M, Berghuis P, Edwards RH, Hioki H, Kaneko T, Mulder J, Canalis JM, Ernfors P, Chaudhry FA, Harkany T. (2006) Vesicular glutamate transporter 3 (VGLUT3) identifies spatially segregated excitatory terminals in the rat substantia nigra Eur.J.Neurosci. (in press)

9. Nielsen T, Bjørås M, Luna L, Slettebakk R, Dale HA, Seeberg E, Rollag H. (2006) Human cytomegalovirus infection modulates DNA base excision repair in fibroblast cells Virology. (in press)

10. Persson S, Boulland JL, Aspling M, Larsson M, Fremeau RT, Edwards RH, Storm-Mathisen J, Chaudhry FA, Broman J. (2006) Distribution of vesicular glutamate transporters 1 and 2 in the rat spinal cord, with a note on the spinocervical tract. J.Comp. Neurol. (in press)

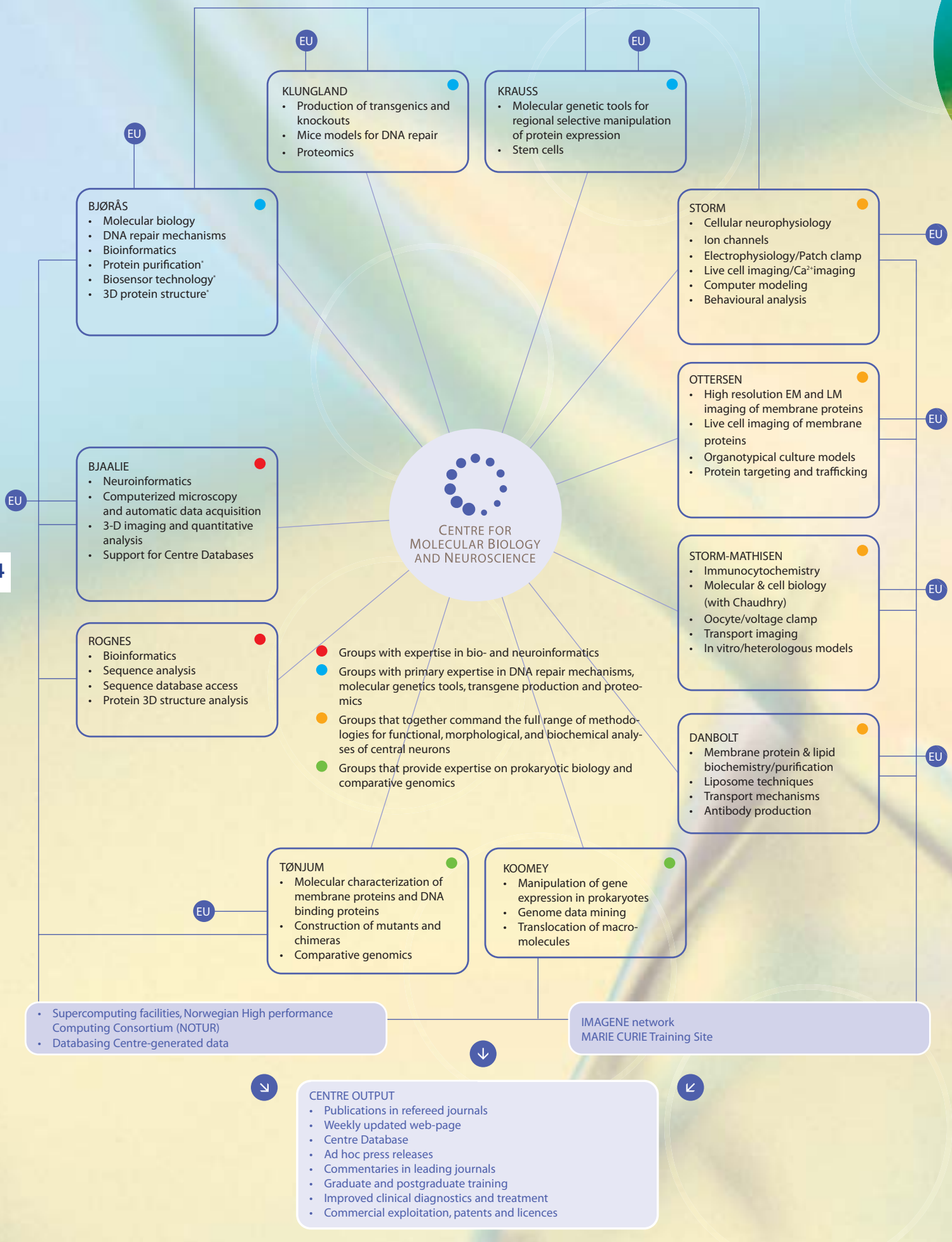
11. Puwarawuttipanit W, Bragg AD, Frydenlund DS, Mylonakou MN, Nagelhus EA, Peters MF, Kotchabhakdi N, Adams ME, Froehner SC, Haug FM, Ottersen OP, Amiry-Moghaddam M. (2006) Differential effect of alpha-syntrophin knockout on aquaporin-4 and Kir4.1 expression in retinal macroglial cells in mice. Neuroscience 137:165-175.

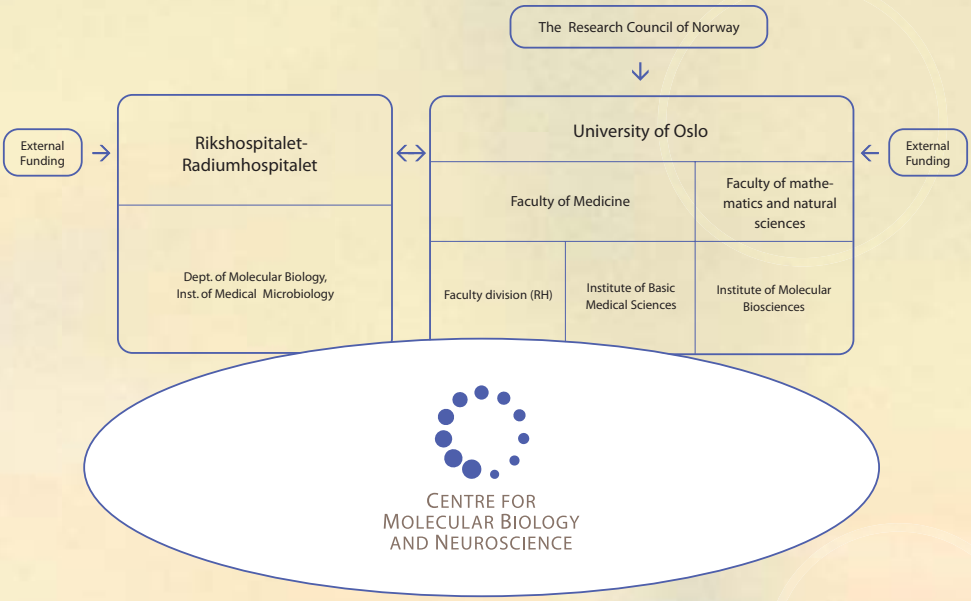
12. *Ringvoll J, Nordstrand LM, Våge CB, Talstad V, Reite K, Aas PA, Lauritzen KH, Liabakk NB, Bjørk A, Doughty RW, Falnes PØ, Krokan HE, Klungland A (2006). Repair deficient mice reveal mABH2 at the primary oxidative demethylase for repairing 1meA and 3meC lesions in DNA. EMBO J. (in press).

13. Rødland EA (2006) Exact distributions of word counts in shuffled sequences. Advances in Applied Probability, 38. (in press)

14. * Vervaeke K., Hu H., Graham, L., Storm J.F. (2006) Contrasting effects of the persistent Na+ current on neuronal excitability and spike timing. Neuron 9: 257-270.

15. *Warskulat U, Borsch E, Reinehr R, Heller-Stilb B, Monnighoff I, Buchczyk D, Donner M, Flogel U, Kappert G, Soboll S, Beer S, Pfeffer K, Marschall HU, Gabrielsen M, Amiry-Moghaddam M, Ottersen OP, Dienes HP, Haussinger D. (2006) Chronic liver disease is triggered by taurine transporter knockout in the mouse. FASEB J. 2006 Mar;20(3):574-6. Epub 2006 Jan 18.


EU
KLUNGLAND
• Production of transgenics and knockouts
• Mice models for DNA repair
• Proteomics
EU
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
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
• 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 (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 2005 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 2005 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

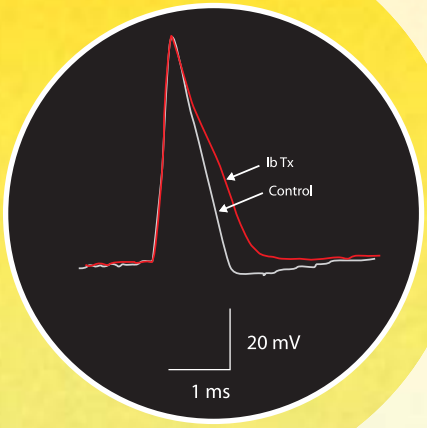
The board was re-appointed in 2005 with one new member. Thus, strategy director Stein Vaaler replaced Inger Nina Farstad, RR. The Board is responsible for ensuring that CMBN is developed in accordance with the current research plan and budget. The members are:

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. In total, more than 135 people are involved in the research at CMBN. In 2005 Magnar Bjørås was appointed as group leader after Erling Seeberg. The Groups in 2005 were:

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 and characterized: that the persistent sodium current, INaP, paradoxically amplifies afterhyperpolarizations 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); the cellular and subcellular distributions and pre- and postsynaptic functions of BK- and SK-type Ca^{2+}-activated K^+ channels (*J Neurosci* 21:9585, 2001; *J Neurosci* 22:9698, 2002; J Physiol 536: 809, 2001).

Prof. Johan F. Storm
Dept. of Physiology and Centre for Molecular Biology and Neuroscience | University of Oslo | POBox 1103 Blindern | N-0317 Oslo | Norway
jstorm@basalmed.uio.no | Phone: +47 22 85 12 46 | Fax: +47 22 85 12 49 | http://folk.uio.no/jstorm

Laboratory for Molecular Neuroscience

Subcellular localization of aquaporin-4 (AQP4) in perivascular astrocyte endfeet. Arrowhead shows endfoot membrane facing the capillary endothelium.

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 explores the pathophysiology of Alzheimer's disease and temporal lobe epilepsy. One of the long term goals is to identify new molecular targets for neuroprotective strategies in stroke and other conditions involving glutamate excitotoxicity.

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.

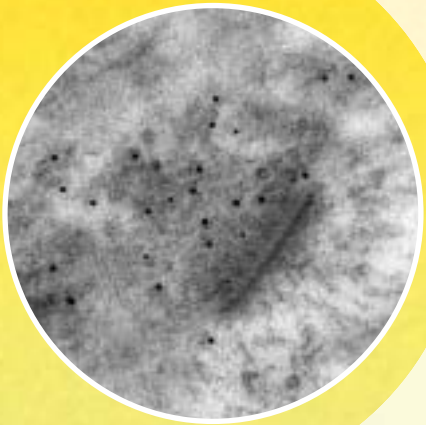
Projects

- 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 may in patients with temporal lobe epilepsy (Lancet, 363:28-37, 2004; PNAS 102:1193-8, 2005).

Prof. Ole P. Ottersen
Dept. of Anatomy and Centre for Molecular Biology and Neuroscience | University of Oslo | POBox 1105 Blindern | N-0317 Oslo | Norway
o.p.ottersen@medisin.uio.no | Phone: +47 90 13 26 10 | Fax: +47 22 85 12 99 | http://folks.uio.no/juniks.no

The Synaptic Neurochemistry Laboratory



A (rare) hippocampal nerve ending with two different glutamate transporters VGLUT1 (big dots) and VGLUT2 (small dots) in its synaptic vesicles (V Gundersen).

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) and modified (Science 2004). The observation that even astrocytes (Nature Neurosci 2004) 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, versus 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, including animal models of neurological disease (e.g. epilepsy).

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

Prof. Jon Storm-Mathisen / Dr. Linda H. Bergersen / Dr. Farrukh A. Chaudhry / Dr. Vidar Gundersen
Dept Anatomy and Centre for Molecular Biology and Neuroscience | University of Oslo | P.O. Box 1105 Blindern | N-0317 Oslo | Norway
jonsm@medisin.uio.no / l.h.bergersen@medisin.uio.no / f.a.chaudhry@biotek.uio.no/ vidar.gundersen@medisin.uio.no
Phone: +47 22 85 12 58 / +47 22 85 14 96 / +47 22 84 05 65 | Fax +47 22 85 12 78
http://folk.uio.no/jonsm/ | http://www.cmbn.no/group-storm-mathisen.html

The Neurotransporter Group

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 500 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

Prof. Niels Chr. Danbolt
Dept. of Anatonomy & Centre for Molecular Biology and Neuroscience | University of Oslo | P.O. Box 1105 Blindern | N-0317 Oslo | Norway
n.c.danbolt@basalmed.uio.no | Phone: +47 22 85 12 60 / +47 22 85 10 41 | Fax: +47 22 85 12 78 | www.neurotransporter.org

NeSys – Neural systems and graphics Computing Laboratory

3-D mapping of body parts in small part of the brain: basis for studying re- organization

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.

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

- Neuroscience image databases. We develop and implement databases and tools in collaboration with the Central University Computing Services at the University of Oslo, Centre Guest Professor Shankar Subramaniam at the San Diego Supercomputing Center, and multiple contributing laboratories in Europe and the USA.

- Digital atlasing; localization in the brain. We develop and use digital atlases for efficiently assigning locations to neuroscience data.

- Brain map transformations. Our research includes studies of brain map transformations and systems level organization, with use of digital atlases and databases. We employ mouse models for studying changes in architecture and design of circuits and regions in the brain, following external and genetic manipulations.

Key achievements: Development of neuroinformatics tools for advanced visualization and mathematical analysis of architecture at multiple levels (e.g., J Neurosci. 18:10603-18, 1998; Proc Natl Acad Sci U S A. 98:6441-6, 2001). Implementation of brain atlas systems allowing continued and dynamic use of published data (Nature Rev Neurosci. 3:322-5, 2002; Neuroscience 2005, 136:681-696) and contributions to science policy developments in this field (Neuroinformatics 1:149-166, 2003). Principles of map transformations in major macrocircuits of the brain (J Neurosci. 20:8474-8484, 2000; J Comp Neurol. 478: 306-322, 2004; J Neurosci. 25:5680-5690, 2005).

Prof. Jan G. Bjaalie
Dept. of Anatomy and Centre for Molecular Biology and Neuroscience | University of Oslo | P.O. Box 1105 Blindern | N-0317 Oslo | Norway
j.g.bjaalie@basalmed.uio.no | Phone: +47 22 85 12 63 / +47 917 87 901 | Fax: +47 22 85 10 45 / +47 22 85 12 78 | www.nesys.uio.no

The Bioinformatics Group

About

The Bioinformatics group uses computational methods to analyse genome sequences both to identify new genes and to determine their function. Advanced statistical and computational tools are used and developed to find patterns or particular sequences that indicate the presence of genes and regulatory elements. In order to identify new relationships between genes, methods are being developed to compare sequences and complete genomes. The group is also creating databases with information about genes of particular interest, e.g. genes involved in DNA repair.

Model of the 3-dimensional structure of a human protein that repairs damaged DNA

Challenges

Sequencing centres around the world have now determined the complete genome sequences of more than 300 organisms. These efforts have resulted in huge amounts of sequence data that are still growing rapidly. The challenges are to find out in detail what genes and other signals these sequences consist of, and what the form and function of the gene products are. Computational analyses of the sequences can often answer many of these questions, and is a great help for later experimental biochemical work. The group is therefore working closely with other groups that study genes using advanced molecular biology methods.

Projects

- **Sequence similarity searches:** Novel tools (e.g. PARALIGN) for particularly rapid and sensitive sequence database similarity searches have been developed and are now available at www.paralign.org on the Internet. Parallelisation and advanced hardware features are exploited to get the highest performance.

- **DNA repair genes:** 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.

- **Structural bioinformatics:** In collaboration with crystallographers and biochemists we are creating computational models of the 3D structure of proteins by homology modelling and fold recognition. We concentrate on DNA repair enzymes and selected groups of membrane proteins. We also do docking and molecular dynamics simulations.

- **Non-coding RNA genes:** The group develops computational methods to identify new non-coding RNA genes (ncRNA). We also try to predict their function. Genome tiling arrays are used to study transcription in “intergenic” regions.

- **DNA variation:** We are studying single nucleotide polymorphisms (SNPs) in DNA repair genes and selected other proteins. How and where do polymorphisms in the human genome occur?

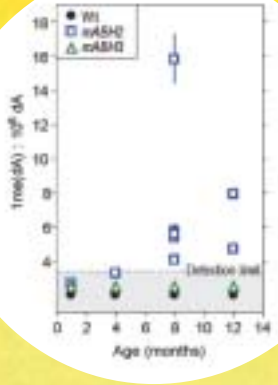
- **Statistical sequence analysis:** Analysis of the abundance and distribution of over- and under-represented oligonucleotides in genomic sequences has led to interesting findings, and we are working on building better statistical models for sequences.

Recent achievements

Created a rapid parallel implementation of the Smith-Waterman sequence alignment algorithm (Bioinformatics 2000); developed PARALIGN - a rapid and sensitive new sequence similarity search tool (NAR 2001) and established PARALIGN web server (NAR 2005). Classified bacterial AlkB repair enzymes (Res. Microbiol. 2003); analysed skewed distribution of DNA uptake sequences in bacterial genomes (NAR 2004) and discovered a new protein superfamily that includes two novel alkylpurine DNA repair glycosylases (Mol. Microbiol. 2006).

Assoc. prof. Torbjørn Rognes
Centre for Molecular Biology and Neuroscience | Institute of Medical Microbiology | Rikshospitalet-Radiumhospitalet | NO-0027 Oslo | Norway
torbjorn.rognes@medisin.uio.no | Phone: +47 90755587 or +47 22844787 | Fax: +47 22844782 | www.cmbn.no/rognes

The Genomic (in)stability Group



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

About

DNA repair is essential for protection against cancer and other age related diseases. Such diseases are believed to be initiated by mutations and rearrangements of the DNA sequence. DNA damage generated by ionising radiation, endogenous alkylating or endogenously hydrolytic and oxidative processes and such damage is efficiently correct by different DNA repair mechanisms in repair proficient cells.

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 of DNA damage. In 2004-2005 several new and exiting models were established. Such models aim to elucidate the contribution of single genes for protection against mutations, genomic instability, ageing and ageing related diseases such as cancer. Several collaborations, internationally and within the Centre for Molecular Biology and Neuroscience, have been initiated.

Projects

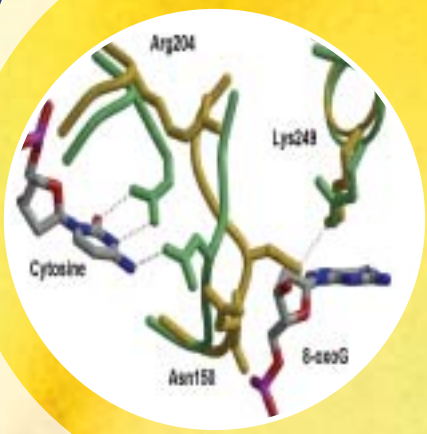
- **Genomic (in)stability:**
  We have established several cell lines and mice carrying null mutations for specific DNA repair functions. These lines include FEN1 mutants generated by site-directed mutagenesis and targeted to the wild-type gene by homologous recombination. FEN1 E160D (approximate 10% enzyme activity remaining) is viable and develop normally until 12 months of age. A high proportion of older mice develops lymphoma. Nevertheless, initial attempts (collaboration with M. Neuberger, Cambridge, UK) failed to identify altered hyperrecombination of immunoglobuline genes. Another model (PCNA interaction domain of FEN1 mutated) is lethal, and cell lines are currently being established from such embryos.

  New gene-targeted models include three novel genes in the new mammalian AlkB family (ABH1-8). We have successfully targeted ABH1, 2 and 3. It was documented that ABH2 is the primary repair gene for 1meA and 3meC damages in genomic DNA, and that 1meA accumulates in untreated *mABH2* knockout mice (see enclosed figure).

- **DNA repair deficiency and brain development:**
  In collaboration with C. McMurray, Mayo Clinic, Rochester (and M. Bjørås, CMBN), we have undertaking a very exiting study which have identified OGG1 initiated base excision repair as one of the major cause of somatic triplet expansion of CAG Huntington triplets in mice.

Prof. Arne Klungland
Dept. of Molecular Biology | Inst. of Med. Microbiology and Centre for Molecular Biology and Neuroscience | Rikshospitalet | N-0027 Oslo | Norway
arne.klungland@medisin.uio.no | Phone: +47 23074072 | +47 90764922 | Fax: +47 23074061 | http://folk.uio.no/aklungla/

Laboratory for Molecular Biology



Protein conformational changes associated with DNA damage recognition (hOGG1, Yellow: native; green: bound to DNA)

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
- 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
- The WRN premature ageing syndrome and role in DNA recombination

Key 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)

Magnar Bjørås
Institute of Medical Microbiology and Centre for Molecular Biology and Neuroscience, Rikshospitalet University Hospital, N-0027 Oslo, Norway
magnar.bjoras@labmed.uio.no | Phone: +47 23 07 40 59/60 | Fax: +47 23 07 40 61 | www.cmbn.no/seeberg

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, horisontal gene transfer and DNA repair mechanisms requires an interdisciplinary approach of molecular biology, genomics and bacterial physiology. Studies on transformation and components providing genome maintenance in genetic model bacteria are most important for understanding the balance between cellular fitness for survival and disease development (Nature Micro Reviews 2006). At present the group addressing these challenges in molecular and cellular biology and medicine includes eleven 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 Biol Chem 2005).

- 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 (Nucl Acids Res 2004).

- 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.

- 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.

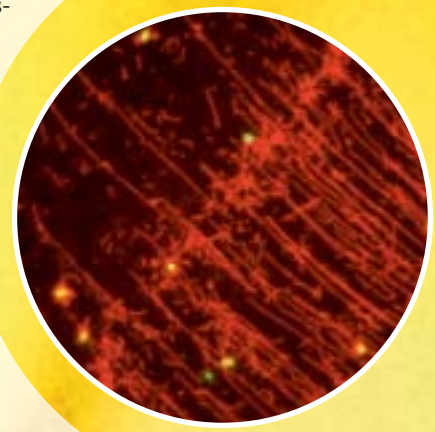
Recent achievements: Secretin PilQ interactions (J Biol Chem 2005), antimutator role of meningococcal MutY and MutS (J Bacteriol 2005; Nature Micro. Rev. 2006)

Prof. Tone Tønjum
Institute of Microbiology and Centre of Molecular Biology and Neuroscience | University of Oslo | Rikshospitalet | N-0027 Oslo | Norway
tone.tonjum@medisin.uio.no | Phone: +47 23 07 40 65 / +47 901 52 936 | Fax: +47 23 07 40 61 | www.cmbn.no/tonjum

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 chosen the human pathogen Neisseria gonorrhoeae, the agent of gonorrhea, as a model system.



N. gonorrhoeae expressing type IV Psendomonas pili (Immunofluorescence 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.

Tfp structure and unique posttranslational modifications: Post-translational modifications (PTMs) are covalent processing events that modify the properties of protein. We recently discovered that the N. gonorrhoeae Tfp pilin subunit protein is posttranslationally modified with the novel moieties phosphoethanolamine and phosphocholine as well as a unique disaccharide. Current goals are to 1) to define the complete repertoire, localization and structure of pilin post-translational modifications, 2) to characterize the biosynthetic pathways by which pilin becomes covalently modified with these novels PTMs and 3) to fully characterize the phenotypes of pilin PTM mutants with regard to pilus biogenesis, structure and function. Recent findings demonstrate remarkable similarities between N. gonorrhoeae Tfp glycosylation and the initial steps in glycan incorporation into eukaryotic glycoproteins. Thus, these studies have a strong potential to enrich our understanding of fundamental biological processes.

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).

Prof. Michael Koomey
Institute of Molecular Biosciences and Centre for Molecular Biology and Neuroscience | University of Oslo | N-0317 Oslo | Norway
j.m.koomey@imbv.uio.no

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

Key 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).

Prof. Stefan Krauss
Institute of Microbiology, Section for cellular and genetic therapy and Centre for Molecular Biology and Neuroscience | Rikshospitalet
N-0027 Oslo | Norway
stefan.krauss@medisin.uio.no | Phone: +47 22 95 81 52 / +47 22 85 12 55 | Fax: +47 22 95 81 51 | www.cmbn.no/krauss/ and www.stemcell.no

FUNDING AND COSTS

The CMBN's income for 2005 of 103 million NOK is up 19 million NOK from 2004, mainly as a result of an increase in the Centre`s external project portfolio. The income is distributed according to the following sources of funding and expenditures:

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

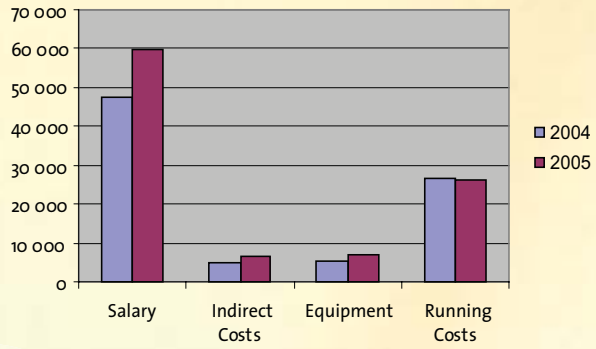
The core CoE funding is provided by the Research Council of Norway (RCN)

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.

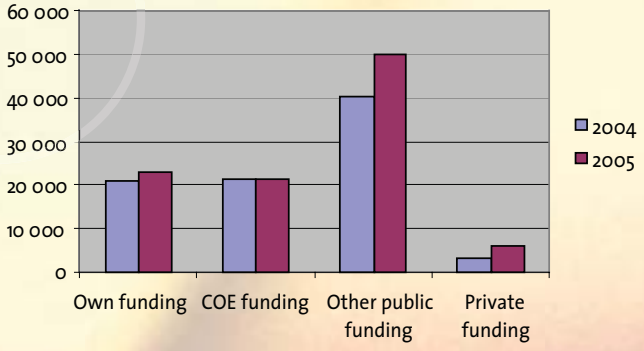
CMBN staff included in 2005 108,8 person years with a salary budget of almost 60 mill NOK. This is up 10 mill NOK from 2004.

Scientific equipment and running costs are crucial to obtain the Centre activities and obligations towards our scientific staff and contractual partners. In 2005 6,8 mill NOK was spent on equipment acquisitions and around 25 mill NOK on running costs and lab supplies.

Funding



Expenditures



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 2005 the staff counted 135 people. If we look at "person years" our statistics shows a stable work force at approximately 108 person years both in 2004 and 2005.

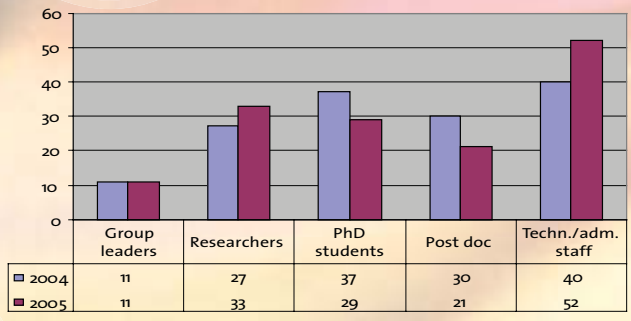
In 2005 the Centre had full time scientists from 14 different countries, including 4 senior researchers, 3 PhD students and 7 Post docs. The Technical staff included 8 foreign citizens. The proportions of men and women in the Centre are almost equal (50 %).

The staff/personnel was divided in different categories as shown. The increase in technical/administrativ staff from 40 in 2004 to 52 in 2005 is caused by changes in budget routines.

In addition to the personnel shown in the figures, 9 "Guest professor" and 35 master and MD students were affiliated with CMBN in 2005, including personnel funded through our Marie Curie Training Sites.

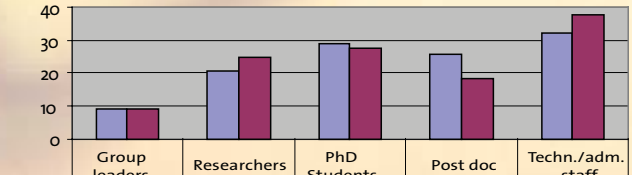
The Centre is constantly focusing on building new international networks by promoting education and mobility. We see this as an important way of recruiting the best candidates.

CMBN staff



	Group leaders	Researchers	PhD students	Post doc	Techn./adm. staff
2004	11	27	37	30	40
2005	11	33	29	21	52

Person month



	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

CMBN

Centre for Molecular Biology and Neuroscience
P.O.Box 1105 Blindern |N-0317 Oslo | Norway

Phone: +47 22 85 14 95
Fax: +47 22 85 14 88

cmbn-adm@medisin.uio.no
www.cmbn.no

design | easy.no