CENTRE FOR MOLECULAR BIOLOGY AND NEUROSCIENCE

ANNUAL REPORT 07

Centre for Molecular Biology and Neuroscience (CMBN)

Norwegian Centre of Excellence

UNIVERSITY OF OSLO

RIKSHOSPITALET

SUMMARY

2007: Setting the stage for CMBN II

2007 was the last year of the first 5-year period of CMBN and the prelude for the Centre's second period 2008 – 2012 (CMBN II). The Centre entered 2007 with much enthusiasm after having passed the midway evaluation with flying colors. The evaluation report – made public in December 2006 - recognized the high productivity of the Centre and concluded *"……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."*

A strategic plan for CMBN II was worked out as part of the midway evaluation process. This plan is comprised of eight work packages, the fulfillment of which depends entirely on the complementary expertise and tight collaboration of the Centre's groups. The group leaders meet on a regular basis to discuss how the new work packages can best be implemented and to identify and rectify possible bottlenecks.

An obvious bottleneck is the lack of space. This bottleneck has existed from the time of the Centre's inauguration in 2002 but has become gradually more noticeable as the Centre has grown and developed. In 2007 the groups of the Centre were spread over five different buildings – a situation not conducive to close scientific interaction. It was therefore with great relief that we received the good news that the University Board had decided – on December 20 last year – to proceed with the plans for the new building just next to Domus Medica. The new building will not be spacious enough to allow the CMBN groups to be co-localized – but it does provide the arena for scientific interaction that we have been missing so deeply ever since the Centre was founded. It is the ambition of CMBN to establish in the new building a range of modern technologies that will serve the scientific environment at large and with a time perspective far beyond 2012 – when our Centre of Excellence will be terminated as a formal entity. The new building should be viewed as the first step in the modernization and strengthening of Life Science research at Gaustad and in the Gaustadbekk valley. The next step will be a Life Science building that is now in the planning stage.

In general terms, the new building next to Domus Medica 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. Undoubtedly, the building will provide a hub for the Gaustad Neuroscience Network (GNN) that was established as a means to promote translational research in Oslo. The technologies that will be included in the new building will bolster the competitive advantage of the research community and help increase the success rate for applications to EU's seventh framework program and other international funding bodies.

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

- High throughput tissue processing
- Structural biology
- Mass spectrometry
- 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)

CMBN will play an active role in building up these facilities as common resources that will outlast by far the lifetime of the Centre.

As described in more detail elsewhere in this annual report, 2007 saw a further extension of CMBN's international networks. Most importantly, CMBN and the Biotechnology Centre of Oslo were included in the Nordic EMBL partnership, forming the Centre for Molecular Medicine Norway (NCMM). The formal signing ceremony took place in Heidelberg on October 3, 2007. Calls for group leaders in NCMM will be opened in spring or summer 2008.

As of 2007, the Biotechnology Centre of Oslo and CMBN are also engaged in EATRIS (European Advanced Translational Research Infrastructure). The ambitious goal of EATRIS is to prepare a Pan-European Infrastructure for translational research. The preparatory phase will last until end 2010 which will mark the beginning of the construction and operation phase of this endeavor.

In 2007, the scientific output of the Centre was larger than ever before, including about 80 articles in international journals. Many of the papers were published in top tier, high impact journals, as described elsewhere in this annual report.

A major milestone was reached by the publication in 2007 of a Special Issue in the journal Neuroscience entitled "Genome Dynamics and DNA Repair in the CNS". The publication of this issue

Ole Petter Ottersen

Tone Tønjum

(edited by Tone Tønjum, Ole P. Ottersen and CMBN guest professor Vilhelm A. Bohr) is an important event in the life of the CMBN because the Issue 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 genome instability and DNA repair with expertise in neurobiology. While the development of new therapies is a long term goal, the Special Issue serves to emphasize the fact that genome instability and DNA repair mechanisms are now centre stage in the field of neurological research. The Special Issue contains numerous papers from CMBN researchers, as well as contributions from leading scientists abroad, and attests to the tight collaborative links that have been established within the Centre.

Finally we would like to take this opportunity to thank the Norwegian Research Council and the funding bodies and host institutions that have supported the activities of the CMBN in 2007. 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 and technical matters.


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HIGHLIGHTS 2007

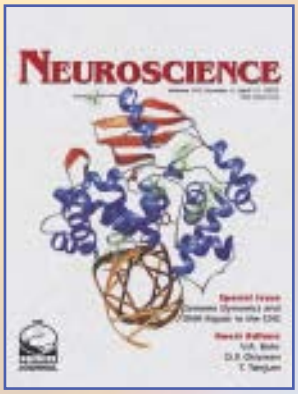
CMBN enters Nordic EMBL partnership

The European Molecular Biology Laboratory (EMBL) was extended in 2007 by a Nordic EMBL partnership with three Institutes of Molecular Medicine located in Umeå, Helsinki and Oslo. CMBN and the Biotechnology Centre of Oslo are associated with the new Centre for Molecular Medicine Norway (NCMM).

The agreement with EMBL was signed in Heidelberg on October 3, 2007 in the presence of the Rector of the University of Oslo (picture).

Neuroscience publishes special issue on Genome Dynamics and DNA Repair in the CNS

In 2007, the journal Neuroscience published a special issue on Genome Dynamics and DNA Repair in the CNS. The issue contained many contributions from CMBN scientists and colleagues. The special issue was edited by Vilhelm A. Bohr, Ole Petter Ottersen, and Tone Tønjum.

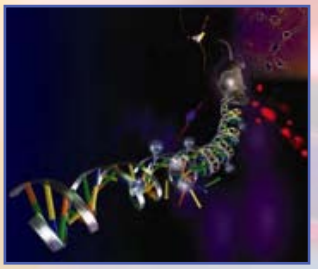


Special Issue: Genome Dynamics and DNA Repair in the CNS Neuroscience, 145 (4), 1183-1448

Publication in Nature on the link between Huntington's disease and DNA repair

Cynthia McMurray's group at the Mayo Clinic, Rochester, MA, USA, and collaborators at NIH and CMBN published in 2007 a study on how DNA repair of oxidative damage is involved in Huntington's disease. The paper explains the role of the 8-oxoguanine-DNA glycosylase (OGG1) enzyme in initiation of age-dependent CAG trinucleotide expansion associated with Huntington's disease.

Kovtun IV, Liu Y, Bjørås M, Klungland A, Wilson, SH & McMurray CT (2007)

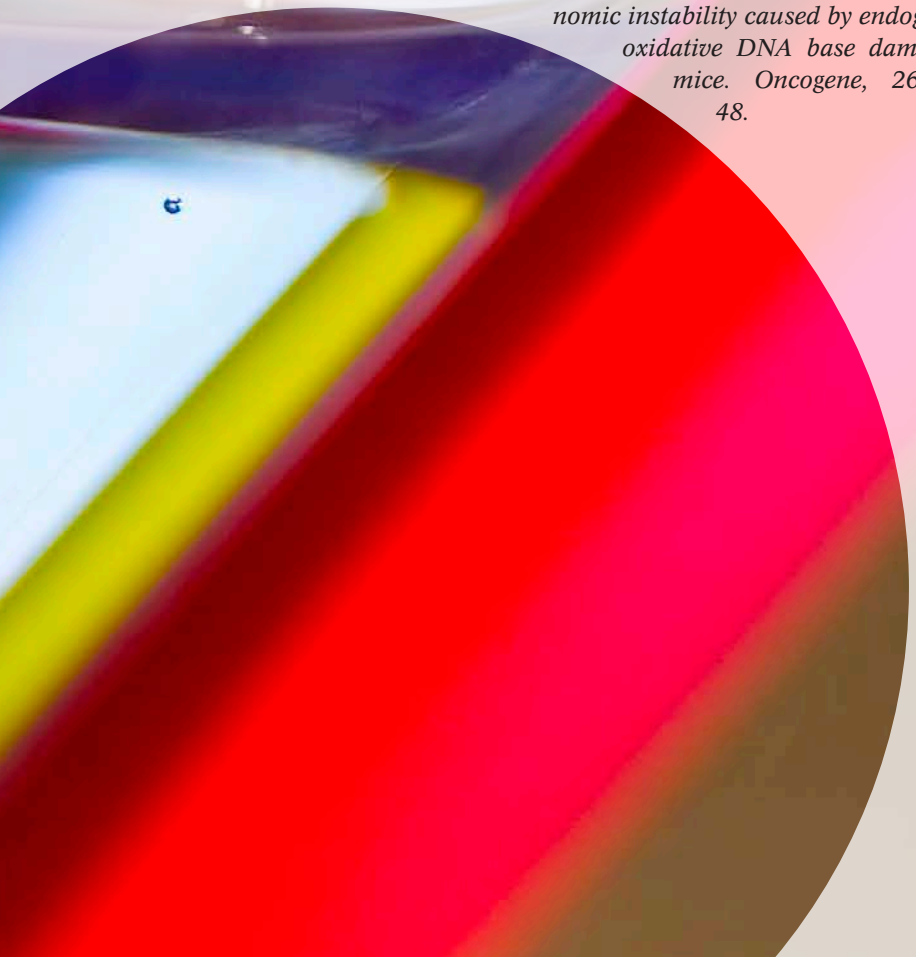


OGG1 initiates age-dependent CAG trinucleotide expansion in somatic cells

HIGHLIGHTS

CMBN chosen as host for National Neuroinformatics Node

The Research Council of Norway appointed in 2007 CMBN as host institution for the Norwegian Node of the newly established International Neuroinformatics Coordinating Facility (INCF). The node is lead by Gaute Einevoll, senior researcher at CMBN and professor at the Norwegian University of Life Sciences, and Johan F. Storm, professor and group leader at CMBN. The node will support national neuroinformatics projects, meetings and courses, and map neuroinformatics activities.



Publication in Oncogene on the Cockayne Syndrome B (CSB) gene

CMBN researchers and collaborators in Germany published in 2007 in **Oncogene** data from a study that indicates that the Cockayne syndrome B (CSB) gene is involved in the inhibition of mutations caused by spontaneous oxidative DNA base damage.

Trapp C, Reite K, Klungland A, Epe B (2007). *Deficiency of the Cockayne syndrome B (CSB) gene aggravates the genomic instability caused by endogenous oxidative DNA base damage in mice. Oncogene, 26,4044-48.*

Publication in Nature Neuroscience on the function of glial glutamate release

CMBN researchers Linda H Bergersen and Vidar Gundersen published in 2007 in **Nature Neuroscience** on the function of glial glutamate release. Synaptic activation of granule cells by the perforant path (the main input to the hippocampus) is enhanced by glutamate exocytosed from astrocytes onto presynaptic NR2B containing receptors. The mechanism is triggered by neuronal activity dependent stimulation of P2Y1 purine receptors on the astrocytes.

Jourdain P[1], Bergersen LH[1], Bhaukaurally K[1], Bezzi P, Santello M, Domercq M, Matute C, Tonello F, Gundersen V[2], Volterra A[2] (2007) *Glutamate exocytosis from astrocytes controls synaptic strength* Nat Neurosci, 10, 331-339
[1]contributed equally; [2]corresponding authors

AWARDS AND DOCTORAL DEGREES

Awards 2007

CMBN scientist Vidar Gundersen receives Monrad-Krohn's Prize 2007. CMBN scientist Vidar Gundersen received the Monrad-Krohn's Prize for 2007. The prize, established in 1933 by professor of neurology, GH Monrad-Krohn, is awarded by the Medical Faculty of the University of Oslo for outstanding neurological research. The award was presented by Professor Rolf Nyberg-Hansen at the annual meeting of the Norwegian Neurological Society, on 30 November 2007. Dr. Gundersen gave his prize lecture on 'Amino acids as signal transmitters at CNS synapses'.

Chaudhry awarded outstanding young investigator grant.
Professor Farrukh A. Chaudry at the Biotechnology Centre of Oslo, University of Oslo, was in 2007 awarded an Outstanding Young Investigator grant ("Yngre Fremragende Forskere" - YFF) from the Research Council of Norway with the project "Physiological and pathological impacts of glutamine transporters". Chaudhry is also a CMBN associated guest professor.

Doctoral degrees 2007

Veslemøy Rolseth defended her PhD dissertation with the title "DNA glycosylases initiating repair of oxidative DNA lesions in mammalian cells". The candidate was supervised by group leader Magnar Bjørås.

Koen Vervaeke defended his PhD dissertation with the title "Effects of sub-threshold activated ion channels on signal integration in hippocampal pyramidal neurons". The candidate was supervised by group leader Johan F. Storm.

Reza Assalkhou defended his PhD dissertation with the title "Meningococcal transformation and type IV pilus biogenesis: Role of PilQ and PilP". The candidate was supervised by co- director and group leader Tone Tønjum.

AWARDS AND DOCTORAL DEGREES

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 and in the Oslo region at large. 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.

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 who acts as a liaison officer between the clinical and basic research departments.

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 five research teams from Norway, Sweden, Denmark, and 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, Germany, 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 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).

Cancer Stem Cell Innovation Centre (CAST) is on of thirteen Centre for Research-based Innovation appointed by the Norwegian Research Council in 2007. CAST is focusing on the concept of small population of stem-like cells being critical in tumour development, and being able to regenerate the whole full-blown tumours on therapy failure or metastasis. CAST is led by CMBN group leader Stefan Krauss.

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. Altogether, 2 seminars and 17 lectures were held in 2007 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.

Seminars

Symposium on "Cellular responses to cellular damage in Schizosaccharomyces pombe" in Oslo

The symposium on Cellular responses to cellular damage in *Schizosaccharomyces pombe* took place in Oslo on 1-4 October 2007. The venue was Holmenkollen Park Hotel in Oslo. The aim was to bring together leading scientists from all over the world on DNA repair, tolerance to DNA damage, modulation of heterochromatin, cell cycle regulation and cell division in fission yeast.

Gaustad Neuroscience Network (GNN) meeting in Oslo

The Gaustad Neuroscience Network (GNN) meeting took place in Oslo on Tuesday 25 September 2007. The main aim of the meeting was to present projects with a translational focus based on cooperation between basic science and clinical research and to heighten the awareness of activities and competence locally in order to increase collaboration and output from ongoing research. At the seminar young researchers with a translational focus on their projects were promoted.

CMBN lectures

Yehezkel Ben-Ari, Founder and Director of the Mediterranean Institute of Neurobiology, Marseille, France, gave a guest lecture on **Thursday 6 December 2007,** with the title: ***Maturation of neuronal activity and networks: 3 universal rules***

Professor Graham AR Johnston, Adrien Albert Laboratory of Medicinal Chemistry, Department of Pharmacology, The University of Sydney, Australia, gave a guest lecture on **Tuesday 20 November 2007,** with the title: ***Modulation of GABA receptors by natural and synthetic flavonoids***

Associate professor David W. Ussery at the Centre for Biological Sequence Analysis (CBS), BioCentrum-DTU, Technical University of Denmark, gave a guest lecture on **Monday 29 October 2007**, with the title: ***PanGenomics of BioTerrorism Bacteria***

Yoshinori Fujiyoshi, Graduate School of Science, Kyoto University, Japan, gave a guest lecture on **Monday 29 October 2007**, with the title: ***Structure and function of multifunctional channels***

Dan Greitz, Karolinska University Hospital, Stockholm, Sweden, gave a guest lecture on **Monday 29 October 2007,** with the title: ***A systems analysis of the CSF with new aspects on transcapillary transport***

Associate Professor Tinna Stevnsner, Danish Centre for Molecular Gerontology, Department of Molecular Biology, University of Aarhus, Denmark, gave a guest lecture on **Thursday 4 October 2007**, with the title: ***Nuclear and mitochondrial DNA repair and relations to aging***

Professor Cynthia McMurray, Department of Molecular Pharmacology and Experimental Therapeutics, and Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, Minnesota, USA, gave a guest lecture on **Monday 1 October 2007**, with the title: ***Genetics and pathophysiology of Huntington's disease***

Professor David Largaespada is the leader of the Genetic Mechanisms of Cancer Program in the University of Minnesota Cancer Center and holds the Margaret Harvey Schering Land Grant Chair in Cancer Genetics. He gave a guest lecture on **Wednesday 19 September 2007**, with the title: ***Transposons for genome engineering and analysis***

Andreas Engel, Professor at the Müller Institute for Structural Biology, Biozentrum, University of Basel, Switzerland, gave a guest lecture on **Tuesday 11 September 2007**, with the title: ***The atomic structure of aquaporins***

Christian Alzheimer, Physiologisches Institut, Christian-Albrechts-Universität zu Kiel, Germany, gave a guest lecture on **Thursday 21 June 2007** at 1530 in the library, Dept. of Physiology, Domus Medica, University of Oslo, with the title: ***Novel functions of acetylcholine and activin in hippocampal signaling and plasticity. Insights from transgenic mice***

Alain Destexhe, Unite de Neurosciences integratives et computationelles, CNRS, Gif Sur Yvette, France, gave a guest lecture on **Wednesday 20 June 2007**, with the title: ***Cortical dynamics during 'active' brain states: How to deal with stochastic activity?***

EDUCATION AND INTERACTION ACTIVITIES

Dr. **Gary Banker**, Center for Research on Occupational and Environmental Toxicology Oregon Health and Science University, USA, gave a guest lecture on **Monday 11 June 2007**, with the title: ***Membrane trafficking and neuronal polarity***

Associate professor **Eva S. Anton**, University of North Carolina, School of Medicine, UNC Neuroscience Center and the Dept. of Cell and Molecular Physiology, gave a guest lecture on **Friday 8 June 2007**, with the title: ***Mechanisms of neuronal differentiation in the developing cerebral cortex***

Professor and guest researcher av CMBN **Vilhelm A. Bohr**, chief, Laboratory of Molecular Gerontology, National Institute on Aging, NIH, US, gave a guest lecture on Thursday, 31 may 2007, with the title: ***Oxidative damage processing, aging and neurodegeneration***

Professor Ian D Duncan, University of Wisconsin – Madison, USA, gave a guest lecture on **Tuesday 13 March 2007**, with the title: ***Cell replacement strategies in MS and the childhood genetic disorders of myelin***

Adam B Robertson, University of North Carolina at Chapel Hill, USA, gave a guest lecture on **Thursday 22 February 2007**, with the title: ***Unraveling the very short patch repair mechanism in E. coli***

Professor Beate Averhoff, Institute of Molecular Biosciences, Johann Wolfgang Goethe Universität Frankfurt, Germany, gave a guest lecture on **Thursday 25 January 2007**, with the title: ***DNA uptake machineries: unique systems for the transport of macromolecules across bacterial membranes***

Professor Sigve Håvarstein, University of Life Sciences, Ås, gave a guest lecture on **Thursday 25 January 2007**, with the title: ***DNA release during natural competence in Streptococcus pneumoniae: altruistic suicide or predation?***

The Centre's lecture series for 2007 was supplemented by seminars under the auspices of affiliated units in the two host institutions (UiO and Rikshospitalet HF). In addition there were open lectures under the auspices of each individual group at the Centre.

CMBN PhD student group activities 2007

In 2007 the PhD student group arranged two scientific meetings and one social event for CMBN members, all in the spring semester.

In March Paul H Backe and Lars Eide gave lectures on protein crystallization/detection and mitochondria/ATP/respiration respectively, before taking us into the clinical biochemistry lab to look at the new Xray diffractometer and the Oxygraph. The meeting ended with pizza and discussion, talking about plans for 2007, scientific and social in the group, and how to get more of the CMBN PhD students to join the group arrangements.

Our second scientific meeting was held in June, with Torleiv Ole Rognum at Rettsmedisinsk inst. (Institute of Forensic Medicine) giving a lecture on "Identification work following mass catastrophe". Professor Rognum has been involved in ID work following catastrophes like Scandinavian Star and the big tsunami in Asia a few years ago. Directly following the lecture, we arranged a social night (pictures) at the Institute of Microbiology, with all the CMBN members invited, for taco and quiz, which was very popular.

Also in 2007, some of the CMBN PhD students and other members were represented in Holmenkollstafetten, and new of the year: Birkebeinerløpet (pictures).

We have throughout the years also been around in the different departments, and visited most of the groups.

Guest Professors

CMBN "Guest Professors" is an important element in the Centre's strategy for academic cooperation. This cooperation is funded mostly through the Centre's CoE grant. In 2007 the following six "Guest Professors" were associated with the Centre:

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

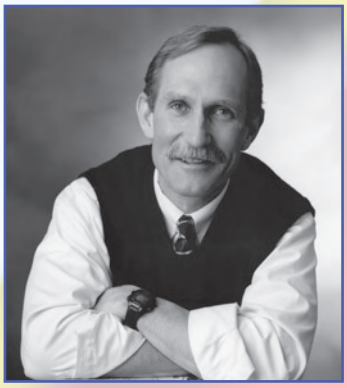
Vilhelm Bohr, Chief of Laboratory of Molecular Genetics, National Institute on Aging, NIH, Baltimore. Funded by CMBN.

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

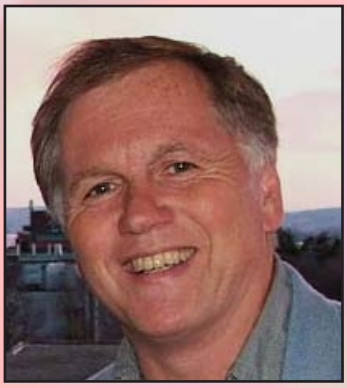
Pål Falnes, Professor at the Institute of Molecular Bioscience, University of Oslo. Funded by CMBN.

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 A. Bohr

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™

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.

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 is 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.

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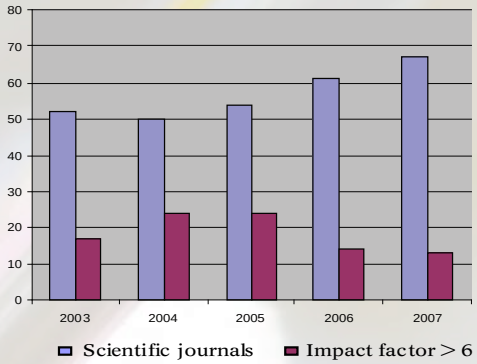
PUBLICATIONS

JANUARY 07 – DECEMBER 07

Abstracts not included

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



1. Adzhubei AA, Vlasova AV, Hagen-Larsen H, Ruden TA, Lærdahl JK, Høyheim B (2007) **Annotated expressed sequence tags (ESTs) from pre-smolt Atlantic salmon (Salmo salar) in a searchable data resource**. BMC Genomics, 8, 209.

2. Alvestad S, Goa PE, Qu H, Risa Ø, Brekken C, Sonnewald U, Haraldseth O, Hammer J, Ottersen OP, Håberg A (2007) **In vivo mapping of temporospatial changes in manganese enhancement in rat brain during epileptogenesis**. Neuroimage, 38, 57-66.

3. Alvestad S, Hammer J, Eyjolfsson E, Qu H, Ottersen OP, Sonnewald U (2007) **Limbic Structures Show Altered Glial-Neuronal Metabolism in the Chronic Phase of Kainate Induced Epilepsy**. Neurochem Res Feb; 33 (2) :257-66

4. Ambur OH, Frye SA, Tønjum T (2007) **New functional identity for the DNA uptake sequence in transformation and its presence in transcriptional terminators**. J Bacteriol, 189, 2077-85.

5. Assalkhou R, Balasingham S, Collins RF, Frye SA, Davidsen T, Benam AV, Bjørås M, Derrick JP, Tønjum T (2007) **The outer membrane secretin PilQ from Neisseria meningitidis binds DNA**. Microbiology, 153, 1593-603.

6. Balasingham SV, Collins RF, Assalkhou R, Homberset H, Frye SA, Derrick JP, Tønjum T (2007) **Interactions between the lipoprotein PilP and the secretin PilQ in Neisseria meningitidis**. J Bacteriol, 189, 5716-27.

7. Benfenati V, Amiry-Moghaddam M, Caprini M, Mylonakou MN, Rapisarda C, Ottersen OP, Ferroni S (2007) **Expression and functional characterization of transient receptor potential vanilloid-related channel 4 (TRPV4) in rat cortical astrocytes**. Neuroscience, 148, 876-92.

8. Bergersen LH (2007) **Is lactate food for neurons? Comparison of monocarboxylate transporter subtypes in brain and muscle**. Neuroscience, 145, 11-9.

9. *Bjaalie JG, Grillner S (2007) **Global neuroinformatics: the International Neuroinformatics Coordinating Facility**. J Neurosci, 27, 3613-5. (Impact factor 7.5)

10. Bjørnsen LP, Eid T, Holmseth S, Danbolt NC, Spencer DD, de Lanerolle NC (2007) **Changes in glial glutamate transporters in human epileptogenic hippocampus: inadequate explanation for high extracellular glutamate during seizures**. Neurobiol Dis, 25, 319-30.

11. Blomberg KE, Smith CI, Lindvall JM (2007) **Gene expression signatures in primary immunodeficiencies: the experience from human disease and mouse models**. Curr Mol Med, 7, 555-66.

12. Bohr VA, Ottersen OP, Tønjum T (2007) **Genome instability and DNA repair in brain, ageing and neurological disease**. Neuroscience, 145, 1183-6.

13. Bohr VA, Ottersen OP, Tønjum T (eds.) (2007) **Special Issue: Genome Dynamics and DNA Repair in the CNS** Neuroscience 145(4):1183-1448. Special Issue.

14. Bolstad I, Leergaard TB, Bjaalie JG (2007) **Branching of individual somatosensory cerebropontine axons in rat: evidence of divergence**. Brain Struct Funct, 212, 85-93.

15. Boulland JL, Ferhat L, Tallak Solbu T, Ferrand N, Chaudhry FA, Storm-Mathisen J, Esclapez M (2007) **Changes in vesicular transporters for gamma-aminobutyric acid and glutamate reveal vulnerability and reorganization of hippocampal neurons following pilocarpine-induced seizures**. J Comp Neurol, 503, 466-85.

16. Buntup D, Skare O, Solbu TT, Chaudhry FA, Storm-Mathisen J, Thangnipon W (2007) **beta-Amyloid 25-35 peptide reduces the expression of glutamine transporter SAT1 in cultured cortical neurons**. Neurochem Res (in press).

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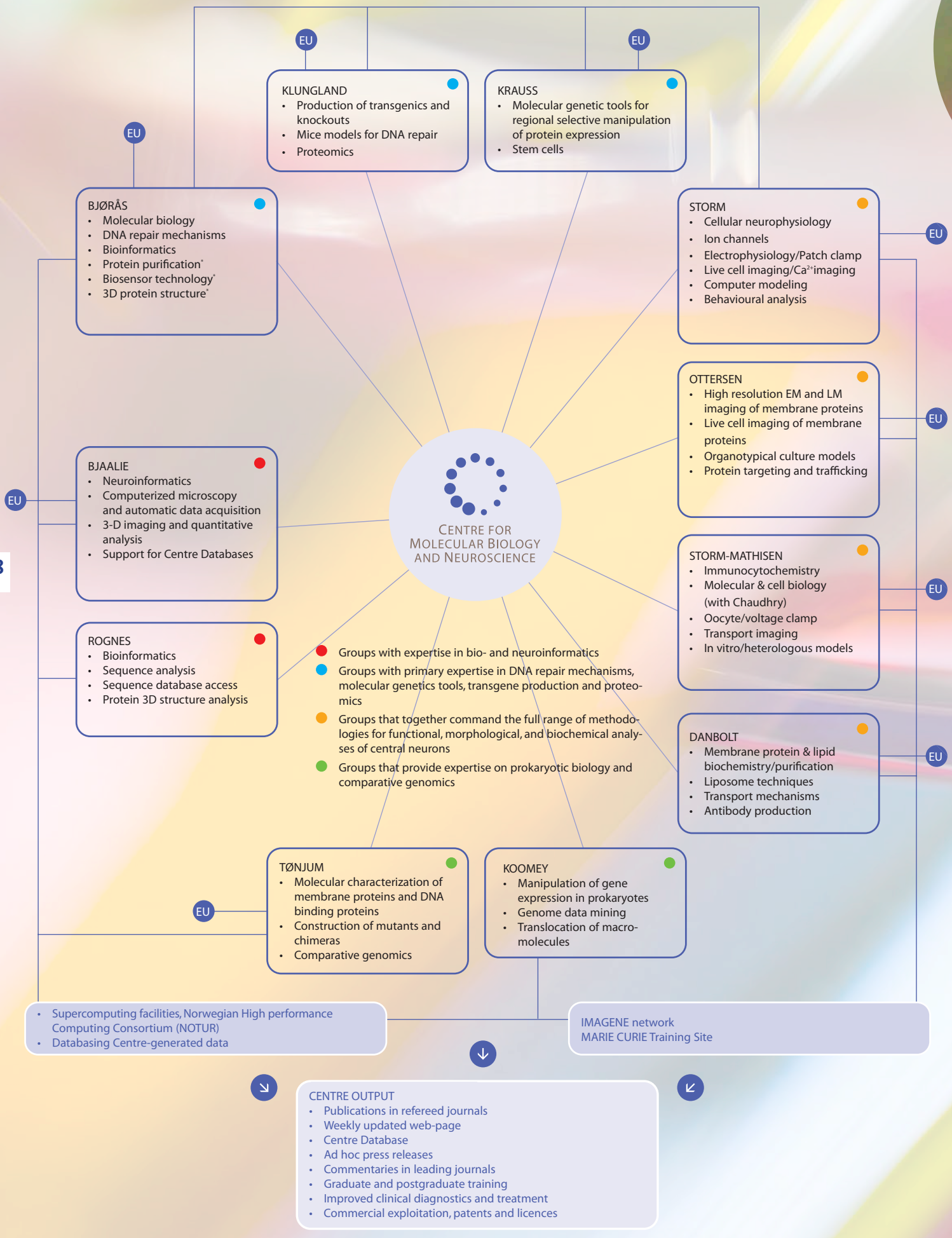
EU
KLUNGLAND
• Production of transgenics and knockouts
• Mice models for DNA repair
• Proteomics
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KRAUSS
• Molecular genetic tools for regional selective manipulation of protein expression
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BJØRÅS
• 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
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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
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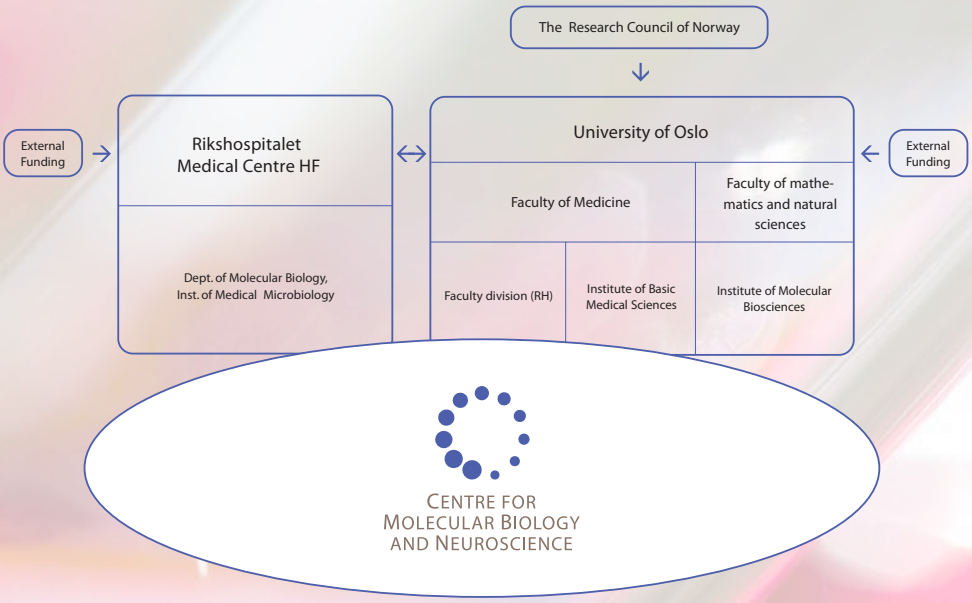
TØNJUM
• Molecular characterization of membrane proteins and DNA binding proteins
• Construction of mutants and chimeras
• Comparative genomics
KOOMEY
• Manipulation of gene expression in prokaryotes
• Genome data mining
• Translocation of macromolecules
• Supercomputing facilities, Norwegian High performance 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 Medical Centre (RH) 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 RH, 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 is headed by Ole Petter Ottersen (Director) and Tone Tønjum (Assistant Director). The Centre has a Steering Group who meets on a regular basis. This group consists of the eleven group leaders of the consortium.

For 2007 the Centre's activities were mainly located in DOMUS MEDICA and the Research Building at RH, at Gaustad. The groups led by Krauss, Koomey, and Rognes are located on other premises at the University Campus.

The board

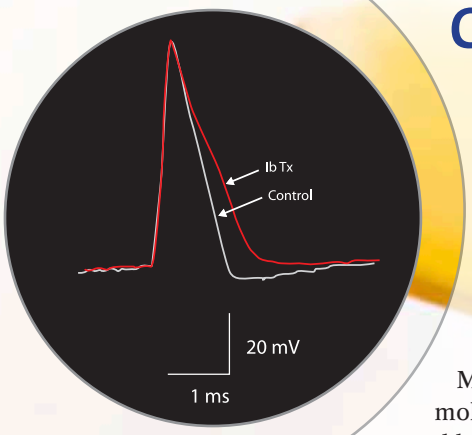
The Board is responsible for ensuring that CMBN is developed in accordance with the current research plan. The members are:

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 HF
Head of Department Peter Gaustad
Rikshospitalet HF
Professor Borghild Roald
University of Oslo

Research groups

The Centre consists of 11 research groups at the University of Oslo (UiO) and Rikshospitalet Medical Centre (RH). 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 150 people are involved full time or part time 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 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).

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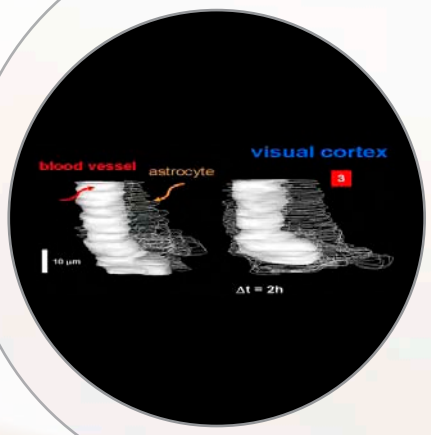
Laboratory for Molecular Neuroscience



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).

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.

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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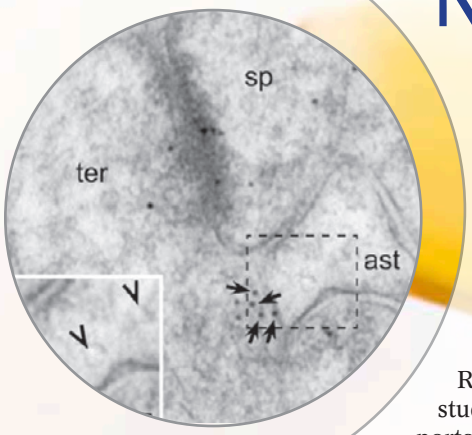
The Synaptic Neurochemistry



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 (see Achievements) has opened possibilities for studying in depth aspects of nervous system functions in health and disease. Important aspects are how nerve endings provide glutamate for synaptic release and how they recover released glutamate for reuse, as well as how synapses provide energy for synaptic transmission and how glial cells can modulate neuronal function. Our main aim is to study synaptic function under physiological conditions and to investigate how the factors contributing to normal signalling are altered in disease, identifying new therapeutic strategies.

Projects

- Role of metabolic precursors of glutamate, including, glutamine, for keeping up synaptic release.
- Interplay of glutamate with other neurotransmitters (e.g. aspartate, GABA, dopamine), including in experimental models of neurological disease (e.g. Parkinson's disease, epilepsy, ADHD).
- Roles of lactate in synaptic transmission and myelinisation studied in monocarboxylate transporter knock-out mice.
- Signalling at the neuromuscular junction: the roles of glutamate and lactate.
- Identification of gliotransmitters and their roles in neuron-glia communication.
- Synaptic changes during ontogenetic development and aging, and in animals with deficient DNA repair.

Recent achievements: 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) were molecularly identified and characterized. A role of glutamine has been defined for normal synaptic function (J Neurochem 2007) and a potential target uncovered in Alzheimer's disease (Neurochem Res 2007). The ultrastructural localization of monocarboxyltate transporters (Cereb Cortex 2005, Neuroscience 2007) provides new approaches to understanding brain 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 in health and disease (J Comp Neurol 2004, 2006, 2007) and modified by gene knock-out (Science 2004). Astrocytes, triggered by purinergic receptors (Eur J Neurosci 2007), release glutamate from VGLUT containing vesicles to enhance synaptic efficacy (Nature Neurosci 2004, 2007). The observations that even astrocytes and non-neural cells (J Cell Sci 2004, J Lipid Res 2007) store and can release neurotransmitter amino acids in a way resembling synaptic release, and that oligodendrocytes have NMDA receptors (Nature 2005), together with findings that glutamate and other neuroactive substances can be co-released from nerve endings (Eur J Neurosci 2003, Molec Neurosci 2004), including at the neuromuscular junction (Neurosci 2007), suggest novel ways of intercellular communication and potential drug targets.

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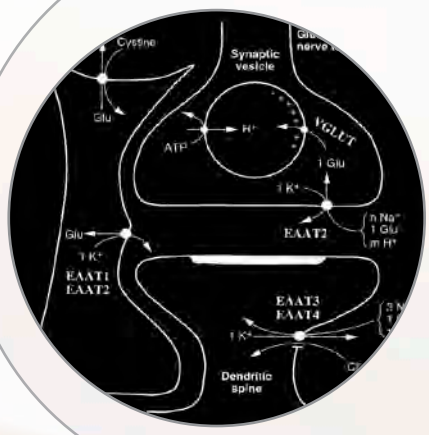
The Neurotransporter Group



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

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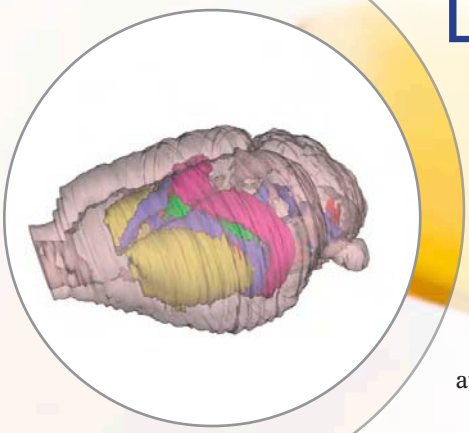
NeSys – Neural systems and graphics Computing Laboratory



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 novel 2-D and 3-D digital atlas systems for assignment of anatomical location and efficient evaluation of spatial distribution patterns present in histological and tomographical images covering the whole rodent brain (Boy et al., NeuroImage 2006; 33: 449-462; Hjørnevik et al., Frontiers in Neuroinformatics 1:4 doi: 10.3389/neuro.11/004.2007; 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: 2801-2812; Leergaard and Bjaalie, Frontiers in Neuroscience 1:211-223, 2007). **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 5:35-58, 2007; www.rodentbrainworkbench.org).

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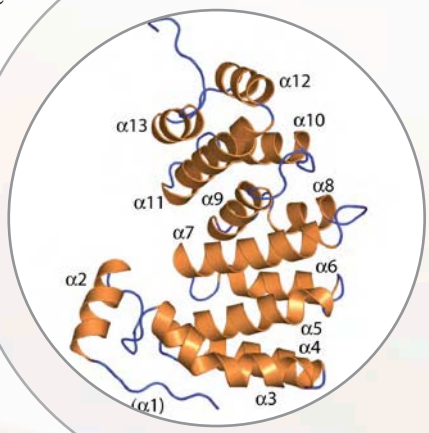
The Bioinformatics Group

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: Discovered a new protein superfamily of glycosylases (Mol. Microbiol. 2006), and analysed their mechanism of repair based on a structural model (NAR 2007). Developed software for annotation of rRNA genes (NAR 2007). Characterized mutations in the PCSK9 gene involved in cholesterol metabolism (J Int Med 2008).

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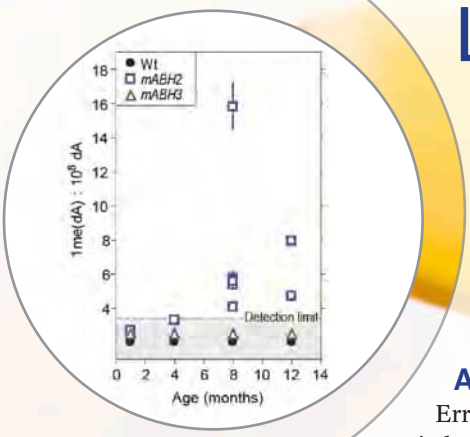
Laboratory for Genome repair and regulation



Scatter diagram showing the level of 1meA in genomic DNA from liver of 1-, 4-, 8- and 12-month-old wild-type, mABH2-and mABH3-targeted mice. Only 8- and 12-month-old mABH2-had 1me(dA)-levels above the detection limit. (Further details in Ringvoll et al., EMBO j 2006).

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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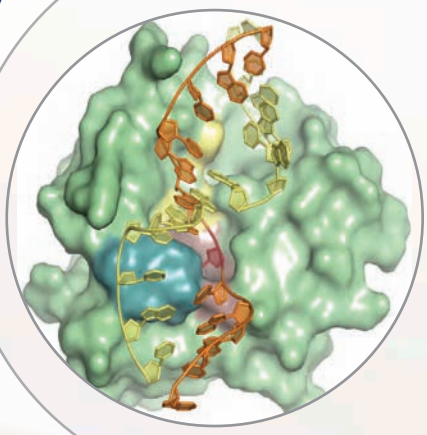
Laboratory for Molecular Biology

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.



Overall structure and DNA conformation of T. maritima EndoV DNA damage (hypoxanthine) recognition complex.

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: Genetics and mechanisms for repair of alkylation damage to DNA (EMBO J 9:4563-8,1990; Nature 421:859-63,2003, NAR 33:1123-31, 2005), 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), structural biochemistry of DNA damage recognition (JMB 317:171-7, 2002; NAR, 37:2451-9, 2007 ; Nature Struct. Biol., 2008) and association between base lesion repair and disease (Blood 105:4730-5, 2005; Nature 447:447-52, 2007). 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)

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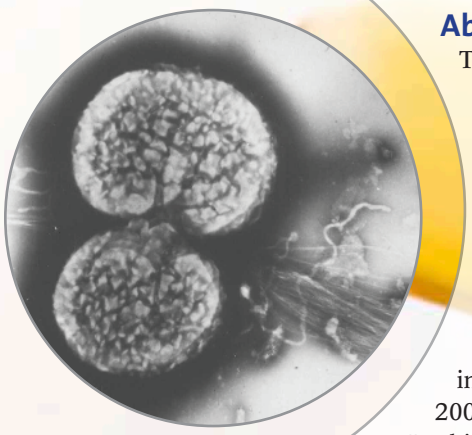
Genome Dynamics and Microbial Pathogenesis



EM image of the meningococcus, a main cause of meningitis worldwide. Bergey's Manual 2006

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 ((J. Bacteriol 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 (PloSOne, 2008).

Recent achievements: Secretin PilQ interactions with DNA (Microbiology 2007), antimutator role of meningococcal MutY and MutS (Nature Micro. Rev. 2006, J. Bacteriol. 2006, 2007), the true identity of the neisseria DNA uptake sequence (J Bacteriol 2007), transformation is conservative and maintains genome stability (Genome Biology, 2008)

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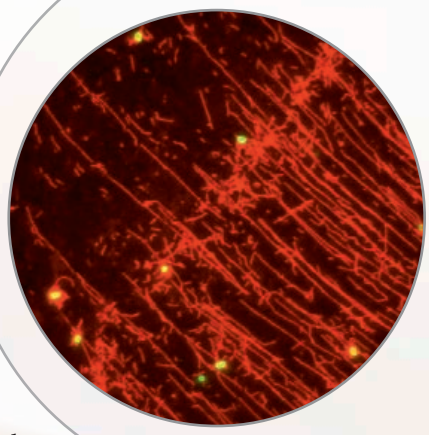
Bacterial Pathogenesis – Molecular and cell Biology

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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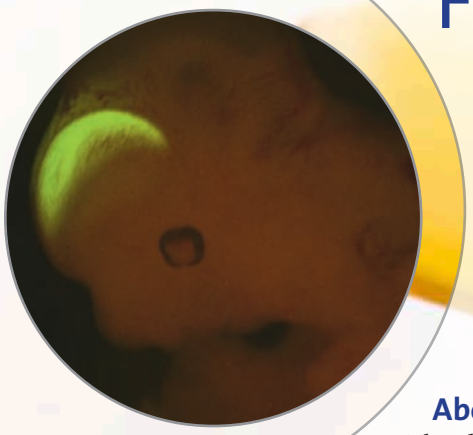
Forebrain development and Neural stem cells



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 COSTS

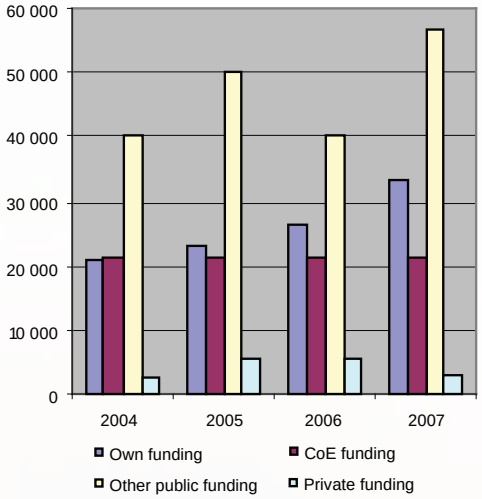
The CMBN's total income for 2007 of 116 million NOK, including 4 million surplus from 2006, exceeds the 2006 income by 15 million NOK, mainly as a result of an increase in the Centre`s external project portfolio. The income is distributed according to the following sources of funding and expenditures:

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

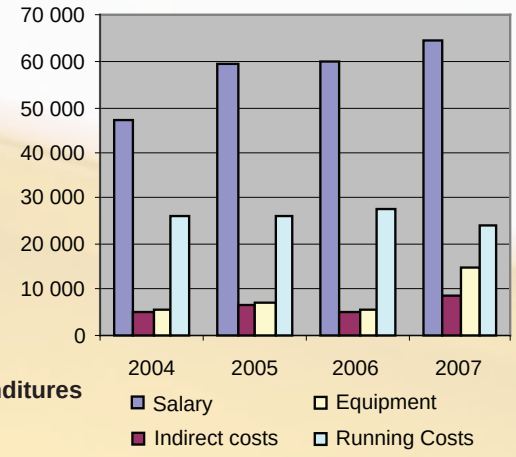
The core CoE funding is provided by the Research Council of Norway (RCN)

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 and the newly appointed Centre of Research Based Innovation.

Funding



Expenditures



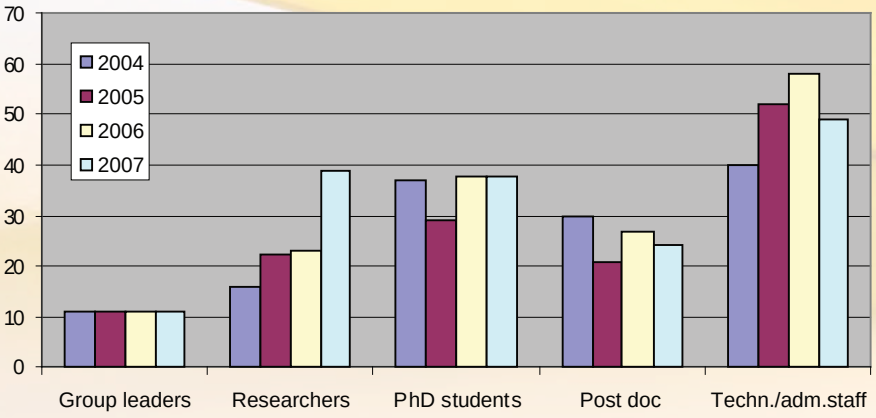
CMBN PERSONNEL AND ASSOCIATED MEMBERS

CMBN policy is to keep our doors open for new and bright people who want to take part in our research activities.

In 2007 the Centre had full time scientists from 12 different countries, including 4 senior researchers, 6 PhD students and 10 Post docs. The Technical staff included 10 foreign citizens. The gender distribution is close to 50/50.

The staff/personnel was divided in different categories as shown. There has been a small reduction in technical/administrative staff in 2007 compared with 2006.

Total staff



In addition to the personnel shown, 6 "Guest researchers" and 32 master and MD students were affiliated with CMBN in 2007, 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.

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