CENTRE FOR
MOLECULAR BIOLOGY
AND NEUROSCIENCE

ANNUAL REPORT 04

Centre for Molecular Biology and Neuroscience (CMBN)

Norwegian Centre of Excellence

UNIVERSITY OF OSLO

Rikshospitalet University Hospital

SUMMARY

2004 was a sad year in the young history of CMBN: Erling Seeberg – preeminent scientist and dear colleague – passed away at the age of 58, on the 14th of December. Erling Seeberg was co-founder and co-director of the Centre and an international leader in the field of DNA repair. His work has received worldwide recognition. Just two months prior to his death, he was awarded the Jahre Prize, the most prestigious Nordic prize in medical research.

Erling Seeberg can never be replaced. But his expertise lives on. He was endowed with a remarkable enthusiasm that helped attract a number of young and talented scientists to his laboratory. His tutorial and personal skills ensured that these talents rapidly developed as independent researchers. Several of these researchers are now group leaders or senior scientists in CMBN, extending Erling's line of research. DNA repair will remain an important focus of CMBN's activities, and basic mechanisms of repair as well as implications for disease, will be topics for further studies - in full agreement with the Centre's work plan. The publication list included with this annual report attests to the impact of CMBN's activities in the field of DNA repair.

Altogether 50 papers were published from the Centre in 2004. It is the policy of the Centre to strive for high visibility on the international arena, and dissemination of results in top tier journals is seen as an important means towards this goal. Close to half of the papers published in 2004 (24 out of 50) appeared in high impact journals, here defined as journals with an ISI impact factor >6. Seven out of the ten papers published so far in 2005 satisfy the same criterion.

Journals selected for CMBN's publications in 2004 included Science (1), Proceedings of the National Academy of Sciences USA (3), Nature Neuroscience (2), Journal of Biological Chemistry (3), Lancet (1), EMBO Journal (1), Molecular Cell (1), Molecular Cell Biology (1), and FASEB Journal (1). The results published in these journals have drawn a number of editorial comments and articles (see "Media" on www.cmbn.no).

The Centre's activity in 2004 has provided significant advances in all of the work packages that comprise the Centre's research plan. As alluded to above, a number of articles have addressed basic mechanisms of DNA repair (refs. 1,6,16-18,27,35,41,46,47,50). There has also been comprehensive activity in research on fundamental microbiological issues including structural and functional aspects of the model organisms Neisseria meningitidis and Neisseria gonorrhoeae (10,11,25,32,33; also see Highlights, p. 3). Several projects – now in process – aim at coupling the Centre's expertise in DNA repair, microbiology and molecular biology to a better understanding of the mechanisms underlying degenerative and infectious diseases of the brain.

Basic neurobiology remains an important field of research in the Centre. Fundamental aspects of glutamatergic transmission have been analyzed (7,8,19,22-24,36). Notably, evidence has been provided that exocytotic release of glutamate is not only a property of neurons but also of brain astrocytes (7). Further, in a paper in Science (19), researchers in CMBN have disclosed that two transporters responsible for glutamate uptake in synaptic vesicles are targeted to functionally distinct synaptic release sites (see Highlights, p. 3).

Research published in 2004 has provided new insight in the expression and function of Ca^{++} activated K^{+} channels in central neurons (21,42,43). Further, the studies of aquaporin water channels in astrocytes have been continued (2-5,30,34). 2004 saw the publication of a Special Issue on brain aquaporins (5), edited by Peter Agre (Nobel Laureate 2003) and researchers at the CMBN.

In line with the vision of the CMBN, the Centre's expertise in basic neurobiology is now being exploited to better understand the mechanisms underlying neurological disease including Alzheimer's dementia (14,28,40,45). Of particular interest is the finding (published in Lancet, ref. 15) that glutamine synthetase (the predominant glutamate-metabolizing enzyme) is downregulated in the hippocampus of patients with mesial temporal lobe epilepsy. This finding may provide an explanation of the loss of glutamate homeostasis that is believed to be an essential pathophysiological aspect of this type of epilepsy. Mesial temporal lobe epilepsy is also known to be associated with a perturbed water homeostasis in the affected areas of the hippocampus. Research in the Centre suggests that this dysfunction may reflect an increase in the tissue level of aquaporin-4 (30).

It should be emphasized that the Centre maintains its high research activity in the field of stem cells and brain development (13,37,39) and that it also strives to advance the methodological repertoire for manipulating the expression levels of proteins in the CNS. The siRNA technology holds great promise in this regard and this technology is now being refined and adapted for *in vivo* use (26,44). Finally, in 2004, the Center assumed responsibility for the establishment of a new small animal PET-imaging facility. Jan Bjaalie, group leader in CMBN, is in charge of this process. The new equipment will be installed in May 2005.

It is with a great deal of optimism and enthusiasm that we are now embarking on the third year of CMBN's existence.

Ole Petter Ottersen
Director

SUMMARY

CMBN HIGHLIGHTS 2004

In a collaborative Oslo-Trondheim study it was shown that a new group of DNA repair enzymes was able to also repair damage on RNA (Aas et al., Nature 2003). In a novel comprehensive study (Ougland et al., Mol Cell 2004) scientists at CMBN demonstrated that a methylation-induced block in the activity of mRNA and tRNA species can be reversed by AlkB (*E. coli*) and hABH3 (human). AlkB-mediated repair of 1-meA in tRNA was observed even in *E. coli in vivo.*

Ougland R, Zhang CM, Liiv A, Johansen RF, Seeberg E, Hou YM, Remme J, Falnes PO AlkB restores the biological function of mRNA and tRNA inactivated by chemical methylation. Mol Cell. 2004 Oct 8;16:107-16.

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Research in CMBN has disclosed new principles for post-translational modifications of proteins, exemplified by the pilus protein of *Neisseria gonorrhoeae.* The discovery of unique posttranslational modifications of pilin with phosphoethanolamine and phosphocholine adds to the complexity of this important virulence factor and provides new insight in the mechanisms of host-pathogen interactions.

Hegge FT, Hitchen PG, Aas FE, Kristiansen H, Lovold C, Egge-Jacobsen W, Panico M, Leong WY, Bull V, Virji M, Morris HR, Dell A, Koomey M. Unique modifications with phosphocholine and phosphoethanolamine define alternate antigenic forms of Neisseria gonorrhoeae type IV pili. Proc Natl Acad Sci U S A. 2004 Jul 20;101(29):10798-803.

First gene knockout of a vesicular glutamate transporter, VGLUT1, shows that the transporter is essential for synaptic transmission (Fremeau et al. 2004, Science, ref. 19, collaboration CMBN-UC San Francisco). Early in development, when the same neurons normally co-express VGLUT2 with VGLUT1, the transmission is nearly normal. Unexpectedly, the same neurons may direct the two transporters to distinct synaptic sites. Loss of VGLUT1 causes a preferential loss of the reserve pool of synaptic vesicles and of synapsin I, suggesting the protein has an additional role in vesicular trafficking.

Editorial comments in Science: "Vesicular Glutamate Transporter--Shooting Blanks" (Perspective by Kim Schuske and Erik M. Jorgensen) Brain activity depends on the release of the neurotransmitter glutamate by exocytosis of synaptic vesicles. Two studies (Fremeau et al., Wocjik et al.) find that mice with the main vesicular glutamate transporter knocked out survive for several months. However, the two studies present different models for subcellular localization of the vesicular transporter and for vesicle loading. (Science 18 June 2004: 1750-1752). "Distinguishing Synaptic Release Sites" Release of the principal excitatory neurotransmitter glutamate depends on its transport into synaptic vesicles by a family of proteins responsible for vesicular glutamate transport. Vesicular glutamate transporters (VGLUT) 1 and 2 have a mutually exclusive distribution in the adult brain. Fremeau et al. now show that earlier in development their distributions overlap and that they mediate glutamate release from distinct synaptic sites made by the same neuron (see the Perspective by Schuske and Jorgensen). Release mediated by the two isoforms also differs in the response to repetitive stimulation, which suggests that there are functional differences between the two release sites. The loss of VGLUT1 selectively reduces the reserve pool of synaptic vesicles and may play a role in membrane trafficking at the nerve terminal. (Science STKE 2004 (238),tw224)

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. The associate editorship of "Neuroscience" - the official journal of the International Brain Research Organization- lies within the Centre (Ole P. Ottersen).

Research courses and lectures

As part of the CoE Programme, the CMBN has undertaken to provide teaching for PhD students and post-doctoral fellows. In 2004 the Centre was awarded formal status as a Research School ("Forskerskole") by the University of Oslo.

Research Course III: "Genome instability and neurologic diseases" (3 credits). The objective of the course was to highlight key aspects of DNA damage and repair in the pathogenesis of neurological disease, and to improve our understanding of how nerve cells communicate in the healthy and diseased brain. Topics addressed were genome instability and maintenance, stem cell biology, brain development, microbial model systems, synaptic communication and informatics/bioinformatics. The new information provided is aimed at building an innovative basis for the development of new approaches for the treatment of brain disease and age-related neurological impairment.

Research Course IV: "Recent advances in Molecular Biology and Neuroscience; Focus on Gaustad Neuroscience Network" (2.5 credits) . The objective of the course was to highlight recent advances related to molecular biology and neuroscience and the pathogenesis and clinical aspects of neurological disease. The course focused on translational research and on current and planned interactions between the basic and clinical research environments that form the Gaustad Neuroscience Network (GNN).

The Cerebellum and Disease Models Workshop at the Norwegian Academy of Sciences in Oslo on May 27th, 2004. The primary goal of this workshop was to initiate a discussion among investigators who are interested in cerebellar function and dysfunction from different perspectives, to explore long term possibilities for synergies at the European level. The workshop also included speakers who are not primarily studying the cerebellum but who have access to methods and approaches that are needed in future cere-bellar research.

Minisymposium: Oxidative DNA damage and repair: Role in cancer and ageing, February 12th, 2004 at Rikshospitalet. Guest lectures: Prof. Barbara Tudek, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland, gave a lecture with the title; *Repair and stability of exocyclic DNA adducts in human cancers*. Prof. Tinna Stevnsner, Laboratory for DNA Repair, Danish Centre for Molecular Gerontology, Dept. Molecular Biology, Aarhus University, Denmark, gave a lecture with the title; *Mitochondrial repair of oxidative damage and changes with aging.*

Homeostasis at brain synapses – options for drug targets. A symposium organized in conjunction with the EU sponsored research project "Dynamics of Extracellular Glutamate" (DECG) and the CMBN, at Losby Gods (near Oslo) September 3-5, 2004. The symposium summarized the achievements of the DECG and central neurobiological research themes of the CMBN. Twenty speakers and 50 participants from the basic and clinical research environment in Norway, Sweden, England, Switzerland, Italy, Slovenia. Abstract book ISBN 82-995010-2-4.

The Marie Curie Training Site in: Basic mechanisms of amino acid neurotransmission (BAMAN), co-ordinator group leader Jon Storm-Mathisen. This EU-financed educational site, hosted by the CMBN, receives students from EU countries for research training as part of the requirement for a PhD degree.

CMBN PhD group activities 2004

The PhD group members meet 2-3 times per semester. They have been visiting all the CMBN departments, at Blindern, Gaustadaléen, Domus medica and Rikshospitalet.

The different groups have presented their labs, offices, equipment, techniques, personal expertise and field of research. Through this strategy they have been introduced to the scientific activities of the CMBN and learnt where to find joint equipment and potential collaborators. This activity has been a powerful tool to integrate our junior scientists into the Centre's overall activities and projects.

The PhD group has arranged a number of social activities, including a cabin trip to Tannlegehytta in Nordmarka and a skiing-trip to Norefjell. The group also participated in Holmenkollstafetten together with other CMBN members.

Guest professors

The recruitment of "Guest professors" is an important element in the Centre's strategy for academic cooperation. This cooperation is funded both through the Centre's CoE grant and through external funds for which special applications are made for appropriate purposes. For 2004 the following visiting researchers were affiliated with the CMBN:

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

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.

Vilhelm Bohr, Chief of Laboratory of Molecular Genetics, National Institute on Aging, NIH, 5600 Nathan Shock Drive, Baltimore, MD 21224, USA.

Hans Krokan, Professor at NTNU, Trondheim. Joint Jahre Prize winner with Erling Seeberg, 2004.

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

CMBN seminars/guest lecturers

Altogether 23 CMBN seminars were held in 2004 with high-profile researchers from abroad as specially invited lecturers. These guest lectures were conducted on the initiative of the Centre management or group leaders. CMBN seminars are held as open lectures and among the places in which they are announced are our Web pages, which are continually updated.

The Centre's lecture series for 2004 was supplemented by seminars under the auspices of affiliated units in the two host institutions. In addition there were open lectures under the auspices of each individual group at the Centre.

CMBN scientific retreat

In 2004 a 2-day seminar was arranged for all staff with affiliation to the Centre, including specially invited guests – the "Granavolden seminar". The number of participants was 80. This annual CMBN retreat with lectures/workshops and discussions at Granavolden contributed to enhanced awareness and interactions between the research groups, not least promoted by very active poster sessions and discussions.

AWARDS AND DOCTORAL DEGREES

Awards 2004

Anders Jahre's award for medical research 2004 was shared between Hans E. Krokan, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology (NTNU) and Erling C. Seeberg, Centre for Molecular Biology and Neuroscience (CMBN), Rikshospitalet and the University of Oslo.

Group leader Jon Storm-Mathisen was awarded **The University of Oslo Research Award 2004** and Mahmood Amiry-Moghaddam in Ole Petter Ottersen's group was given **His Majesty the King's gold medal 2004** for the best doctoral thesis at the Faculty of Medicine.

Doctoral degrees 2004

Cand.scient. Jean-Luc Boulland: "Recycling the amino acid neurotransmitter glutamate in the CNS: L'alchimie du glutamate et de la glutamine". Thèse en cotutelle: Université Pierre et Marie Curie, Paris, Institute of Basic Medical Sciences & Centre for Molecular Biology and Neuroscience. Supervision by Farrukh A. Chaudhry / Group leader Jon Storm-Mathisen.

M.Sc. Mattias Backman: "Characterisation of the functions of Dachshund 1 and beta-catenin in embryonic brain development in mouse". Institute of Medical Microbiology & Centre for Molecular Biology and Neuroscience. Supervision by group leader Stefan Krauss.

Cand.scient. Randi Margrete Aamodt: "Base excision repair in mutagenesis and ageing". Institute of Medical Microbiology & Centre for Molecular Biology and Neuroscience. Supervision by group leader Erling Seeberg.

Cand.scient. Terje Hegge: "Studies of PilV - a *Neisseria gonorrhoeae* type IV prepilin- like protein involved in human epithelial cell adherence and pilin subunit post-translational modification". Institute of Pharmacy & Centre for Molecular Biology and Neuroscience. Supervision by group leader Michael Koomey.

NETWORKS

Gaustad Neuroscience Network (GNN) has been established to link basic science and clinical research addressing all aspects of neuroscience represented in the Gaustad region. 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. In a longer perspective the GNN is expected to facilitate the development of a multidisciplinary neuroscience research environment with a mass that ensures a high visibility at the international level. New funding will have to be generated to boost 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". CMBN already contributes to GNN by providing administrative and financial support for workshops/meetings and by covering a 20% position that is supposed to liaise the basic and clinical research environment at the Gaustad campus.

International networks

Nordic Centre of excellence (NCoE) for Research in Water Imbalance Related Disorders (WIRED). Coordinator is professor/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 professor and group leader 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 professor and 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 9 partners from Poland, France, England, Denmark and Norway.

COLLABORATING PARTNERS

In 2004 the CMBN had over 40 ongoing co-operative relationships with research communities in numerous countries, of which 28 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 School, 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 Attwell, 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

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 Molleculaire et Cellulaire, GBMC, Strasbourg, France

Cynthia McMurray, Mayo Clinic, Rochester, USA

Piet Borst, The Netherlands Cancer Institute, NCI, Amsterdam, Holland

Oleg Shupliakov, Karolinska Institute, Stockholm, Sweeden

COMMERCIALIZATION

In accordance with the agreements relating to the Centre, the commercialisation of research results emanating from the Centre will be an important element in its future funding. The CMBN commercialization portfolio consisted in 2004 of two projects supported by Birkeland Innovation, which is the Technical Transfer Office 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 sense of genetic data at an accelerated speed (www.sencel.com)

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

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. Our media profile is taken care of by group leader Jon Storm-Mathisen.

PUBLICATIONS

JANUARY 04 – DECEMBER 04

Abstracts not included

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

1. *Alseth I, Korvald H, Osman F, Seeberg E, Bjørås M. A general role of the DNA glycosylase Nth1 in the abasic sites cleavage step of base excision repair in Schizosaccharomyces pombe. **Nucleic Acids Res.** 2004 Sep 27;32(17):5119-25.

2. *Amiry-Moghaddam M, Xue R, Haug FM, Neely JD, Bhardwaj A, Agre P, Adams ME, Froehner SC, Mori S, Ottersen OP. Alpha-syntrophin deletion removes the perivascular but not endothelial pool of aquaporin-4 at the blood-brain barrier and delays the development of brain edema in an experimental model of acute hyponatremia. **FASEB J.** 2004 Mar;18(3):542-4. Epub 2004 Jan 20. (Impact 7.3)

3. Amiry-Moghaddam M, Frydenlund DS, Ottersen OP. (2004) Anchoring of aquaporin-4 in brain: Molecular mechanisms and implications for the physiology and pathophysiology of water transport. **Neuroscience.** 2004;129(4):997-1008.

4. Agre P, Nielsen S, Ottersen OP (2004) Towards a molecular understanding of water homeostasis in the brain. **Neuroscience.** 2004;129(4):849-50.

5. Agre P, Nielsen S, Ottersen OP (2004) (eds) Brain Water Homeostasis. Special Issue. **Neuroscience,** Volume 129, Issue 4, Pages 849-1054.

6. *Aamodt RM, Falnes PO, Johansen RF, Seeberg E, Bjoras M. The Bacillus subtilis counterpart of the mammalian 3-methyladenine DNA glycosylase has hypoxanthine and 1,N6-ethenoadenine as preferred substrates. **J Biol Chem.** 2004 Apr 2;279(14):13601-6. (Impact 6.4)

7. *Bezzi P, Gundersen V, Galbete JL, Seifert G, Steinhauser C, Pilati E, Volterra A. (2004) Astrocytes contain a vesicular compartment that is competent for regulated exocytosis of glutamate. **Nature Neurosci.** 7:613-620. (Impact 15.1)

8. Boulland JL, Qureshi T, Seal RP, Rafiki A, Gundersen V, Bergersen LH, Fremeau RT Jr, Edwards RH, Storm-Mathisen J, Chaudhry FA. Expression of the vesicular glutamate transporters during development indicates the widespread corelease of multiple neurotransmitters. **J Comp Neurol.** 2004 Dec 13;480(3):264-80.

9. Broman J, Rinvik E, Sassoe-Pognetto M, Shandiz HK, Ottersen OP (2004) Glutamate. In: **The Rat Nervous System (Elsevier).** Ed.: G. Paxinos, pp. 1269 1292.

10. *Collins, R.F., S. A. Frye, A. Kitmitto, R. C. Ford, T. Tønjum and J. P. Derrick. Structure of the Neisseria meningitidis outer membrane PilQ secretin complex at 12 Šresolution. **J. Biol. Chem** 2004, 279:39750-6

11. *Davidsen T, Rodland EA, Lagesen K, Seeberg E, Rognes T, Tønjum T. Biased distribution of DNA uptake sequences towards genome maintenance genes. **Nucleic Acids Res.** 2004 Feb 11;32(3):1050-8 (Impact 7.1)

12. de Bilbao F, Arsenijevic D, Vallet P, Hjelle OP, Ottersen OP, Bouras C, Raffin Y, Abou K, Langhans W, Collins S, Plamondon J, Alves-Guerra MC, Haguenauer A, Garcia I, Richard D, Ricquier D, Giannakopoulos P. Resistance to cerebral ischemic injury in UCP2 knockout mice: evidence for a role of UCP2 as a regulator of mitochondrial glutathione levels. **J Neurochem.** 2004 Jun;89(5):1283-92.

13. Diep DB, Hoen N, Backman M, Machon O, Krauss S. Characterisation of the Wnt antagonists and their response to conditionally activated Wnt signalling in the developing mouse forebrain. **Brain Res Dev Brain Res.** 2004 Nov 25;153(2):261-70.

14. Eid T, Brines ML, Cerami A, Spencer DD, Kim JH, Schweitzer JS, MD4; Ottersen OP, de Lanerolle NC. Increased expression of erythropoietin receptor on blood vessels in the human epileptogenic hippocampus with sclerosis. **J Neuropathol Exp Neurol,** 2004, 63:73-83.

15. *Eid T, Thomas MJ, Spencer DD, Runden-Pran E, Lai J, Malthankar GV, Kim JH, Danbolt NC, Ottersen OP, de Lanerolle NC (2004). Loss of glutamine synthetase in the human epileptogenic hippocampus: a possible mechanism for elevated extracellular glutamate in mesial temporal lobe epilepsy. **Lancet,** 2004, 363:28-37. (Impact 15.4)

16. *Falnes PO, Bjoras M, Aas PA, Sundheim O, Seeberg E. Substrate specificities of bacterial and human AlkB proteins. **Nucleic Acids Res.** 2004 Jun 30;32(11):3456-61. (Impact 6.5)

17. *Falnes PO. Repair of 3-methylthymine and 1-methylguanine lesions by bacterial and human AlkB proteins. **Nucleic Acids Res.** 2004 Dec 01;32(21):6260-7.

18. *Foksinski M, Rozalski R, Guz J, Ruszkowska B, Sztukowska P, Piwowarski M, Klungland A, Olinski R. Urinary excretion of DNA repair products correlates with metabolic rates as well as with maximum life spans of different mammalian species. **Free Radic Biol Med.** 2004 Nov 1;37(9):1449-54.

19. *Fremeau RT, Jr., Kam K, Qureshi T, Johnson J, Copenhagen DR, Storm-Mathisen J, Chaudhry FA, Nicoll RA, Edwards RH (2004) Vesicular glutamate transporters 1 and 2 target to functionally distinct synaptic release sites. **Science,** 304:1815-1819. (Impact 29.1)

20. *Gammelsaeter R, Frøyland M, Aragón C, Danbolt NC, Fortin D, Storm-Mathisen J, Davanger S, Gundersen V (2004) Glycine, GABA and their transporters in pancreatic islets of Langerhans: evidence for a paracrine transmitter interplay. **J Cell Sci.** 117:3749-3758. (Impact 7.2)

21. *Grunnet M, Kaufmann WA. Co-assembly of big conductance Ca2+-activated K+ channels and L-type voltage-gated Ca2+ channels in rat brain. **J Biol Chem.** 2004 279:36445-53. (Impact 6.4)

22. Gundersen V, Holten AT, Storm-Mathisen J. (2004) GABAergic synapses in hippocampus exocytose aspartate on to NMDA receptors: quantitative immunogold evidence for co-transmission. **Mol Cell Neurosci.** 26:156-165.

23. *Harkany T, Holmgren C, Härtig W, Qureshi T, Chaudhry FA, Storm-Mathisen J, Fremeau RT, Jr., Edwards RH, Mackie K, Ernfors P, Zilberter Y (2004) Endocannabinoid-independent retrograde signaling at inhibitory synapses in layer 2/3 of neocortex: involvement of vesicular glutamate transporter 3. **J Neurosci.** 24:4978-4988. (Impact 8.3)

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25. *Hegge, F.T., Hitchen, P.G., Aas, F.E., Kristiansen, H., Lovold, C., Egge-Jacobsen, W., Panico, M., Leong, W.Y., Bull, V., Virji, M., Morris, H.R., Dell, A. and Koomey, M. (2004) Unique modifications with phosphocholine and phosphoethanolamine define alternate antigenic forms of *Neisseria gonorrhoeae* type IV pili. **Proc Natl Acad Sci** U S A, **101,** 10798-10803. (track 2) (Impact 10.2)

26. Holen T, Mobbs CV. Lobotomy of genes: use of RNA interference in neuroscience. **Neuroscience.** 2004;126(1):1-7. Review.

27. Larsen E, Kwon K, Coin F, Egly JM, Klungland A.Transcription activities at 8-oxoG lesions in DNA. **DNA Repair (Amst).** 2004 Nov 2;3(11):1457-68.

28. Lechner T, Adlassnig C, Humpel C, Kaufmann WA, Maier H, Reinstadler-Kramer K, Hinterholzl J, Mahata SK, Jellinger KA, Marksteiner J. Chromogranin peptides in Alzheimer's disease. **Exp Gerontol.** 2004 Jan;39(1):101-13.

PUBLICATIONS

29. Leergaard TB, Alloway KD, Pham TA, Bolstad I, Hoffer Z, Pettersen C, Bjaalie JG. Three-dimensional topography of corticopontine projections from rat sensorimotor cortex: Comparisons with corticostriatal projections reveal diverse integrative organization. **J Comp Neurol.** 2004; 478: 306-322.

30. Lee T-S, Eid T, Mane S, Kim JH, Spencer DD, Ottersen OP, de Lanerolle NC (2004) Aquaporin-4 is increased in the sclerotic hippocampus in human temporal lobe epilepsy. **Acta Neuropathol,** (Berl). 2004 Dec;108(6):493-502. Epub 2004 Oct 26.

31. Maghazachi AA, Knudsen E, Jin Y, Jenstad M, Chaudhry FA (2004) D-galactosyl-b1-1' sphingosine and D-glucosyl-b1-1' sphingosine induce human natural killer cell apoptosis. **Biochem Biophys Res Com.** 320:810-815.

32. *Maier, B., Koomey, M. and Sheetz, M.P. (2004) A force-dependent switch reverses type IV pilus retraction. **Proc Natl Acad Sci U S A,** 101, 10961-10966. (track 2) (Impact 10.2)

33. *Morand, P.C., Bille, E., Morelle, S., Eugene, E., Beretti, J.L., Wolfgang, M., Meyer, T.F., Koomey, M. and Nassif, X. (2004) Type IV pilus retraction in pathogenic *Neisseria* is regulated by the PilC proteins. **EMBO J,** 23, 2009-2017. (Impact 10.4)

34. Nagelhus EA, Mathiisen, TM, Ottersen OP Aquaporin-4 in the central nervous system: cellular and subcellular distribution and coexpression with Kir4.1. (2004) **Neuroscience,** 2004;129(4):905-913

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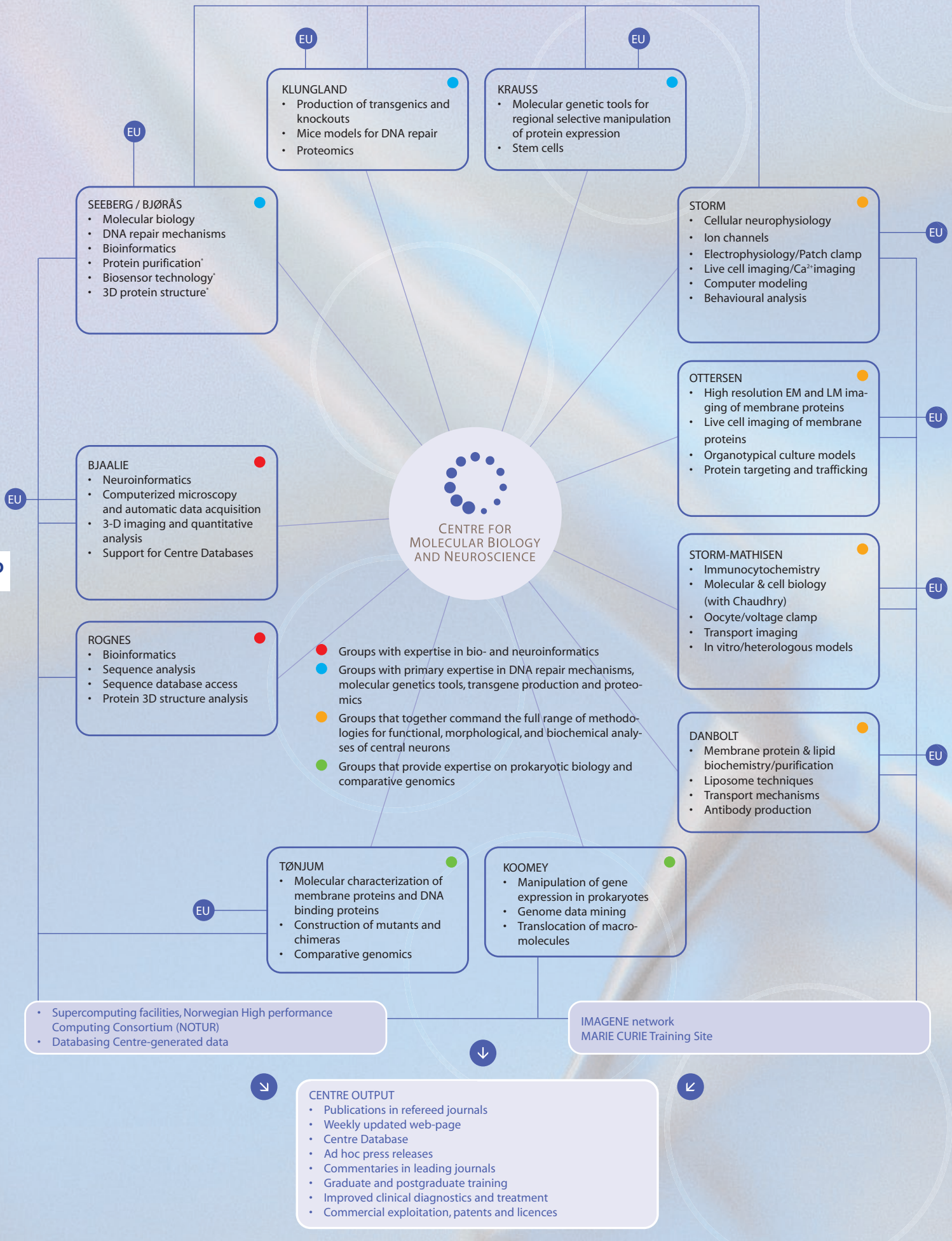

EU
EU
KLUNGLAND
• Production of transgenics and knockouts
• Mice models for DNA repair
• Proteomics
KRAUSS
• Molecular genetic tools for regional selective manipulation of protein expression
• Stem cells
EU
SEEBERG / BJØRÅS
• Molecular biology
• DNA repair mechanisms
• Bioinformatics
• Protein purification*
• Biosensor technology*
• 3D protein structure*
STORM
• Cellular neurophysiology
• Ion channels
• Electrophysiology/Patch clamp
• Live cell imaging/Ca2+imaging
• Computer modeling
• Behavioural analysis
EU
OTTERSEN
• High resolution EM and LM imaging of membrane proteins
• Live cell imaging of membrane proteins
• Organotypical culture models
• Protein targeting and trafficking
EU
EU
BJAALIE
• Neuroinformatics
• Computerized microscopy and automatic data acquisition
• 3-D imaging and quantitative analysis
• Support for Centre Databases
CENTRE FOR MOLECULAR BIOLOGY AND NEUROSCIENCE
STORM-MATHISEN
• Immunocytochemistry
• Molecular & cell biology (with Chaudhry)
• Oocyte/voltage clamp
• Transport imaging
• In vitro/heterologous models
EU
ROGNES
• Bioinformatics
• Sequence analysis
• Sequence database access
• Protein 3D structure analysis
Groups with expertise in bio- and neuroinformatics
Groups with primary expertise in DNA repair mechanisms, molecular genetics tools, transgene production and proteomics
Groups that together command the full range of methodologies for functional, morphological, and biochemical analyses of central neurons
Groups that provide expertise on prokaryotic biology and comparative genomics
DANBOLT
• Membrane protein & lipid biochemistry/purification
• Liposome techniques
• Transport mechanisms
• Antibody production
EU
TØNJUM
• Molecular characterization of membrane proteins and DNA binding proteins
• Construction of mutants and chimeras
• Comparative genomics
EU
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

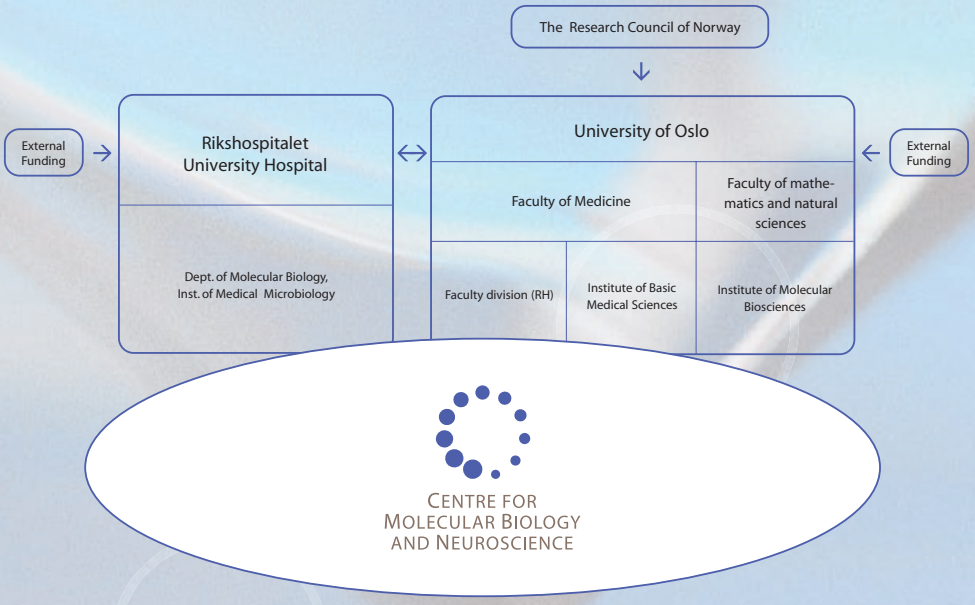
ABOUT CMBN AND THE GROUPS

ABOUT CMBN AND THE GROUPS

The Centre for Molecular Biology and Neuroscience (CMBN) at the University of Oslo (UiO) and Rikshospitalet University Hospital 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 Rikshospitalet, respectively.

Objectives

The Centre shall take on a leading role in elucidating the importance 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 overstimulation 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 2004 led by Ole Petter Ottersen (Director) and Erling Seeberg (Co-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 2004 the Centre's activities were mainly located in DOMUS MEDICA and the Research Building at RH, at Gaustad. In addition, the Krauss, Koomey and Rognes groups are located on other premises in and around the University Campus.

The board

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

Prof. Ole M. Sejersted,
University of Oslo (Chairman)

Director Prof. Olli A. Jänne,
Biomedicum Helsinki, Finland

Director Per Morten Vigtel,
Norsk Investorforum

Senior Adviser Inger Nina Farstad,
Rikshospitalet University Hospital

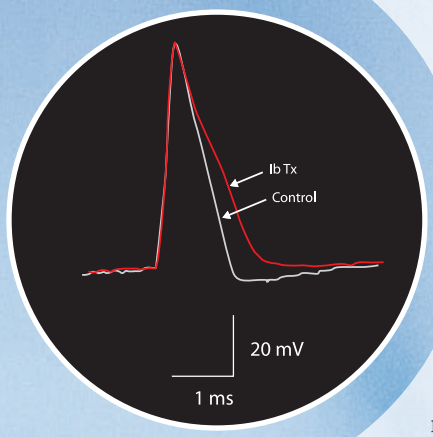
Head of Department Peter Gaustad,
Rikshospitalet University Hospital

Professor Borghild Roald,
University of Oslo

Research groups

The Centre consists of 11 research groups at the University of Oslo (UiO) and Rikshospitalet University Hospital (RH). In total, more than 100 people are involved in the research at CMBN. The Groups in 2004 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 behavior, 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 behavioral 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 neurone.
- 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 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).

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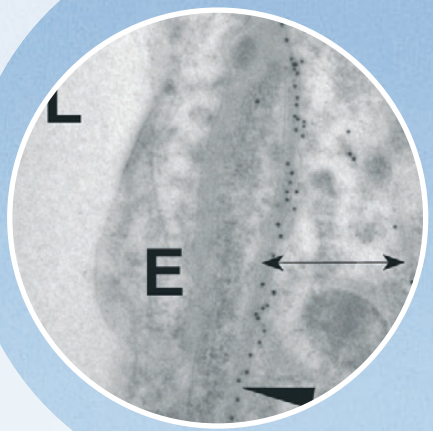
Laboratory for Molecular Neuroscience

About

The Laboratory for Molecular Neuroscience investigates molecular mechanisms involved in the development of acute and chronic neurodegenerative disease, with a focus on the role of glutamate excitotoxicity. It aims at unravelling the molecular basis for cell death and edema development in stroke, and 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.



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

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).

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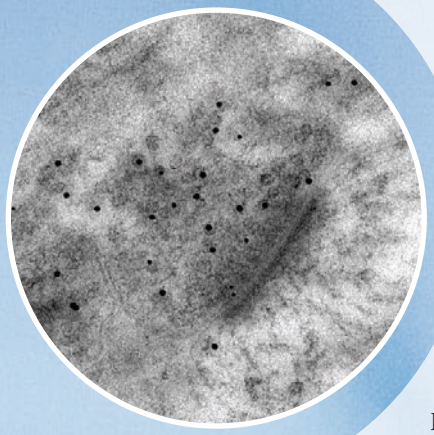
The Synaptic Neurochemistry Laboratory



A rare hippocampal nerve ending with two different glutamate transprorters 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 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 observations that even neuronal dendrites (J Neurosci 2004), astrocytes (Nature Neurosci 2004) and neuroendocrine cells (J Cell Sci 2004) can release glutamate in a way resembling synaptic release, together with findings that glutamate can be co-released with other neuroactive substances (Eur J Neurosci 2003, Molec Neurosci 2004), suggest 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.

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The Neurotransporter Group

The distribution of glutamate transporter proteins

About

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

Challenges

The human genome contains about 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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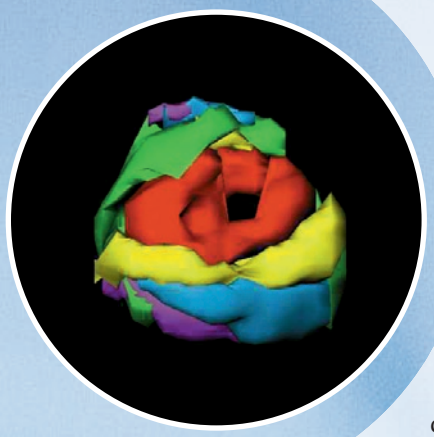
NeSys – Neural systems and graphics Computing Laboratory



3-D mapping of body parts in a 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 (J Neurosci 18:10603-18, 1998). Implementation of relational database and brain atlas systems allowing continued and dynamic use of published data (Nature Rev Neurosci 3:322-5, 2002; Neuroscience 2005, in press) and contributions to science policy developments in this field (Neuroinformatics 1:149-166, 2003). Principles of map transformations in major circuits of the brain (J Neurosci 20:8474-8484, 2000; J Comp Neurol 478:306-322, 2004).

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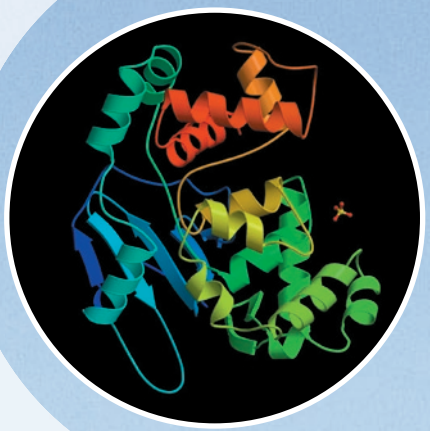
The Bioinformatics Group



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

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.

Challenges

Sequencing centres around the world have now determined the complete genome sequences of more than 200 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 to find genes involved in repair. We are also modelling the 3D structure of selected DNA repair proteins by homology modelling.

- **Non-coding RNA genes:** The group is working to develop methods to identify new members of the interesting class of genes that does not encode proteins, but stable and functional non-coding RNA genes (ncRNA). This includes microRNA, ribosomal RNA and many other types of ncRNA.

- **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: Rapid parallell implementation of the Smith-Waterman algorithm (Bioinformatics 2000); ParAlign - a rapid and sensitive new sequence similarity search tool (NAR 2001); classification of bacterial AlkB proteins (Res Microbiol 2003); skewed distribution of DNA uptake sequences in bacterial genomes (NAR 2004).

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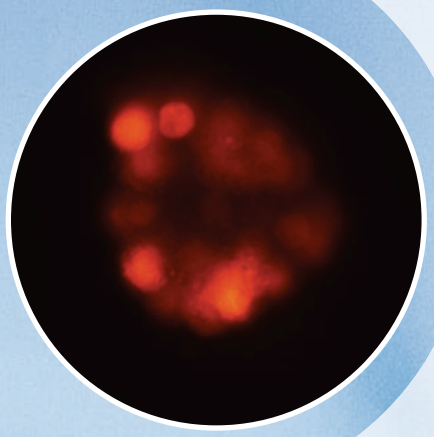
The Genomic (in)stability Group



Induced oxidative stress leads to apoptosis in FEN 1 mutant blastocysts (MCB, 2003)

About

Repair of DNA damage 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, simple alkylating agents or endogenously hydrolytic and oxidative processes is corrected by the base excision repair (BER) pathway.

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. 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

- DNA repair genes: We use homology based sequence analysis to identify and characterise DNA repair genes from mammalian cells.
- Genomic (in)stability: We have established several cell lines and mice carrying null mutations for specific DNA repair functions. Such models, including those supplied by our collaborators, are used to identify genes involved in maintenance of genomic stability.
- Cell and animal models with altered DNA repair capacity: Several new genes for DNA repair have been identified following the publication of the human DNA sequence. We design constructs for targeted mutations of such genes in cells and mice.
- DNA repair deficiency and brain development: Genetic diseases caused by defective DNA repair are almost always associated with neurological abnormalities. Collaborations have been established within the Centre to identify the neurological defects associated with individual DNA repair activities.
- Genomic (in)stability and aging in DNA repair deficient strains of yeast, S. cerevisiae.

Recent achievements: Characterization of enzymes required for repair of base lesions in DNA, by the base excision repair pathway (EMBO J 1997, 16, 3341-3348; Mol Cell 1999, 3, 33-42). Transcription coupled repair of oxidative DNA damage (PNAS 2000, 97, 8397-8402; Mol Cell, 2003, 12, 799-800). Construction of gene-targeted knockout mice (PNAS 1999, 96, 13300-13305; MCB, 2003, 23, 5346-5353).

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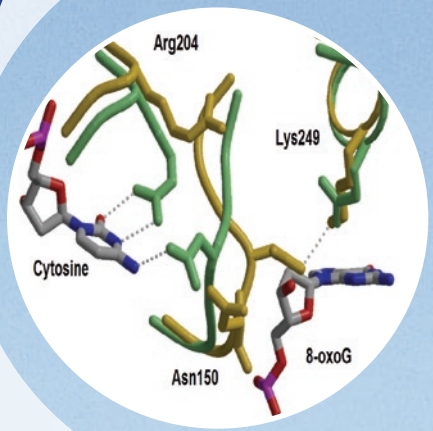
Laboratory for Molecular Biology



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, Blood 2005). Significant contributions have also been made in the fields of brain glutamate transport (Nature 360:464-7,1992, Eur J Nurosci 6:936-42,1994), haematopoiesis (Blood 91:4127-35,1998), and bioinformatics (Bioinformatics 16:699-706,2000)

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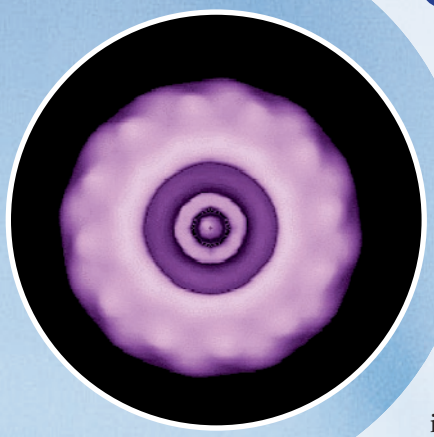
Genome Dynamics and Microbial Pathogenesis



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

About

The stability of microbial genomes and gene pools is constantly challenged by horisontal gene transfer and recombination, as well as DNA damage. Mechanisms for rapid genome variation, adaptation and maintenance are a necessity to ensure microbial fitness and survival in 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 (Trends Microbiol 2001, 2004). Our group addresses these challenges in molecular and cellular biology and medicine 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. In the long run 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 meningitides, or the meningococcus (Mc), 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. We are characterising the structure-function relationships and interactions of components involved in the membrane transport of pili and DNA (Mol Microbiol 1998, JBC 2004, 2005).Effects of the meningococcus (Mc) on brain water homeostasis: By using cellular and animal models the effect of Mc and Mc components on glial aquaporins will be characterized. 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).Intracellular survival of Mycobacterium tuberculosis: Inside the macrophage phagolysozome, M. tuberculosis faces unusually harsh challenges. We are studying the mechanisms for genome maintenance and thereby fitness for survival in the world's biggest bacterial killer.

Recent achievements: Bias of DNA uptake sequences (NAR 2004), secretin PilQ structure (J Biol Chem 2004 and 2005), antimutator role of meningococcal MutY (J Bacteriol 2005)

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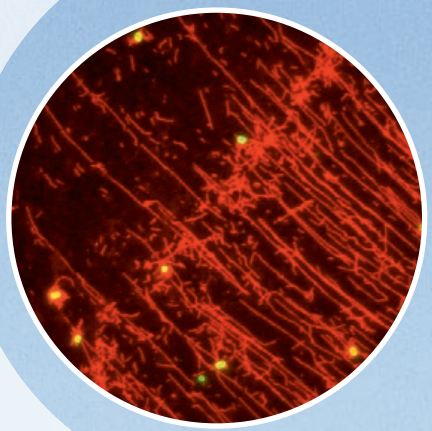
Bacterial Pathogenesis – Molecular and cell Biology

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



N. gonorrhoeae expressing type IV Psendomonas pili (immunofluorescence microscopy - cells / 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).

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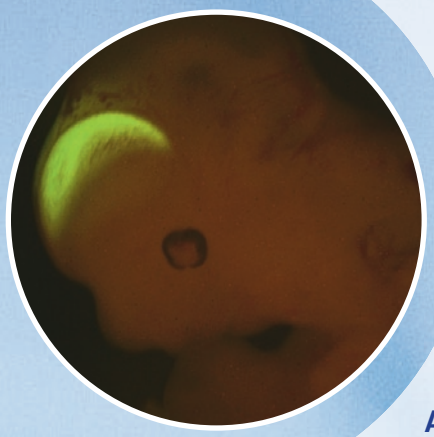
Forebrain development and Neural stem cells



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

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; Brain Res Dev Brain Res 2004). Role of numb for cortical neurogenesis (Nature Neurosci 2004).

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FUNDING AND COSTS

The CMBN's total financial plan for 2004 amounted to NOK 84 million, distributed according to the following sources of funding:

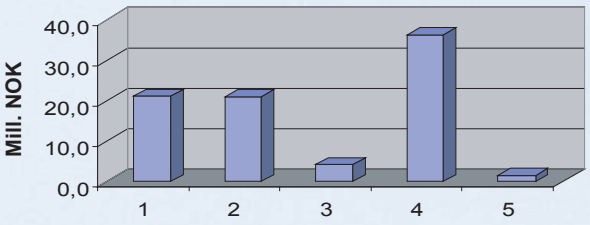
Own funding includes support from our two host institutions, The University of Oslo and The National Hospital, and includes salary, location and running costs.

The CoE funding is provided by the National Research Council (NRC) to the Centre in accordance to our status of Centre of Excellence.

The largest part of the CMBN financial base is funding from other sources, that has been applied for by the different groups. In addition to the CoE funding, the NRC provides funding to the individual groups.

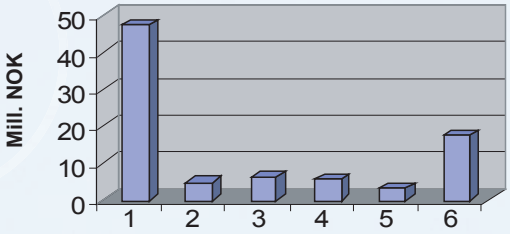
CMBN staff includes 131 people (see below) with a salary budget at almost 50 mill NOK. The Centre emphasizes the need for training and educational activities. In 2004 we spent 9 mill NOK (incl. traveling costs) as an investment to uphold a strong and competitive staff and to educate new researchers.

CMBN funding 2004



1. Own funding	20,8 mill NOK
2. CoE funding	21,1 mill NOK
3. EU funding	4,2 mill NOK
4. Other public funding	35,0 mill NOK
5. Private funding	2,7 mill NOK

CMBN costs 2004



1. Salary	47,4 mill NOK
2. Rent of location etc	4,9 mill NOK
3. Training and education	6,0 mill NOK
4. Equipment	5,6 mill NOK
5. Travel	3,0 mill NOK
6. Lab supplies	17,3 mill NOK

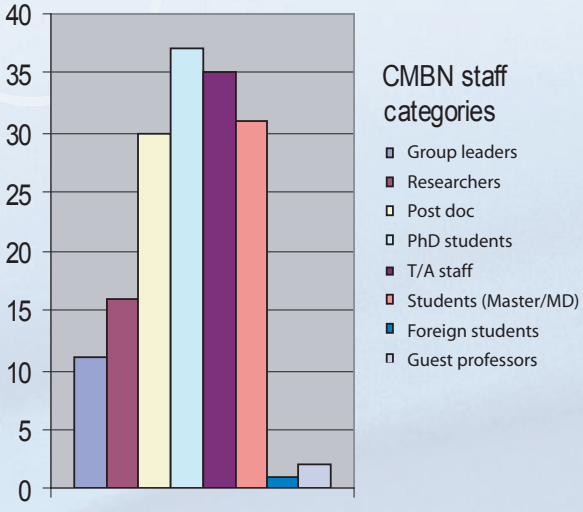
CMBN PERSONNEL AND ASSOCIATED MEMBERS

In 2004 CMBN staff and associated members counted 163 people. Among these, 131 were on the Centre's pay roll. The staff was divided as shown in the figure.

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

In 2004 the Centre had full time scientists from 10 different foreign countries, including 2 senior researchers, 4 PhD students and 5 Post docs. The Technical staff included 5 foreign citizens.

The proportions of men and women in the Centre are almost equal (50 %).



Group leaders	11
Researchers	16
Post doc	30
PhD students	37
Technical/administrative staff	35
Students (Master and MD)	31
Other students (Fulbright)	1
Guest professors/researchers	2
Total	**163**

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