Centre for Molecular Biology and Neuroscience (CMBN)

09

ANNUAL REPORT 2009

CENTRE FOR
MOLECULAR BIOLOGY
AND NEUROSCIENCE

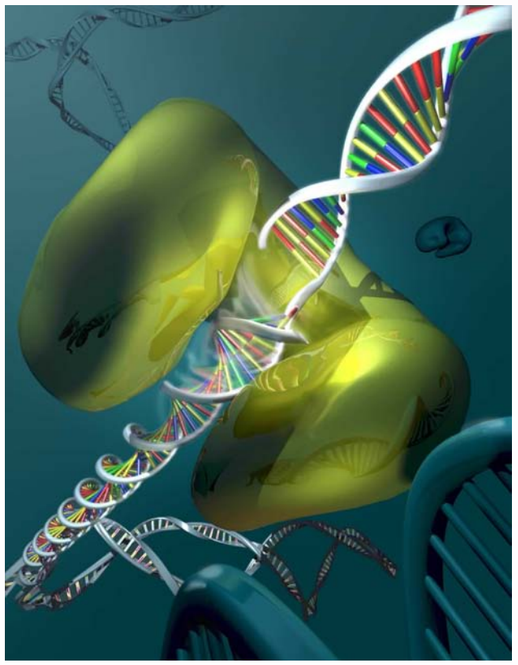
Norwegian Centre of Excellence

UNIVERSITY OF OSLO

Oslo University Hospital

Vision

The vision of the Centre is to be recognized as one of the most innovative research environments to identify, develop and promote new approaches for the treatment of brain diseases and age-related neurological ailments. To achieve the above goal the Centre aims at gaining a thorough understanding of relevant basic biological processes and disease mechanisms.



A topoisomerase enzyme clamps onto a DNA molecule. The enzyme cuts through one of the two strands after which the DNA molecule can spin around in a cavity of the enzyme. (Source: Tremani)

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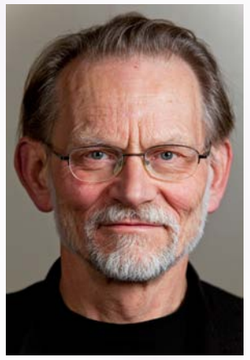
2009 fuelled by new discoveries, networks and innovation

Tone Tønjum



Jon Storm-Mathisen

by Professor Tone Tønjum
Director of the Centre and
Professor Jon Storm-Mathisen
Co-Director

2009 has for CMBN been spiced by ample new scientific discoveries and events, locally and at the international level. These activities all nurture the basic goal of the Centre, to be recognized as one of the most innovative research environments in identifying and developing new methodologies in the diagnostics, prevention and treatment of different brain diseases and age-related neurological ailments. To achieve this goal, the Centre aims at a thorough understanding of basic biological processes in health and disease. While interactions between the eleven groups of the Centre form the cornerstone of major research projects, we are also seeing an increased number of collaborative projects that engage other environments, including other centers of excellence, in Norway and internationally.

Among the keys to success in such a *multidisciplinary environment* are, first of all, to *state the prime questions in current science*, and, secondly, to *evoke an open and adjustable attitude in the interpretation of the findings*. Thirdly, but not the least, the signature of *CMBN is to host unique competence, diversity and complementarity in terms of human resources, scientific qualifications and assets*, and both young and senior scientists are engaged in *internationalization* activities. The CMBN publication record for the years 2002-2009 is evidence of the success of our interdisciplinary approach.

CMBN is in itself an incentive to bridge the disciplinary divides that otherwise can exist in scientific environments. It has catalysed the establishment of new regional and national networks that will generate translational research and innovation. The former Gaustad Neuroscience Network promoting translational research, was expanded, geographically and in terms of scope, to become Oslo Neuroscience Network. We are currently in the process of creating a national innovation cluster in neuroscience, the Nansen Neuroscience Network (NNN), which includes basic and clinical research environments, as well as relevant industrial partners.

The building of the new annexe to Domus Medica is scheduled to commence on June 14, 2010, however, efforts to address the challenge of covering the expenses for scientific equipment were initiated already in 2009. Our goal is to obtain funding for all the technologies that will be allocated in the new building including high throughput tissue processing, mass spectrometry/structural biology, neuro/bioinformatics and transgene technology, and in this context a number of new large funding schemes are pursued. The building and the technologies it will host will serve the strong translational research network we're currently building. The Letten Centre was initiated in March 2009; thanks to a substantial private donation it is now possible to carry out the plans for an imaging centre that also is an integral part of the new EMBL node NCMM, also established in 2009.

Science education is a priority in CMBN, ranging from bachelor and master students to the fostering of new independent scientists. The energy and motivation of our young talents continue to impress. One important measure taken in 2009 is the investment in young talented group leaders to secure their scientific career ahead. We have increased our dedicated efforts to ensure that our most promising young scientists can position themselves for independent funding. This is one significant way of keeping competence on board.

Our own illustrious Centre Director Ole Petter Ottersen was elected Rector of the University of Oslo. We are all impressed with and grateful for his endeavours for CMBN, and are convinced that he will perform superbly in his new post. While all directorships have their own signature and imprint, it is our humble and enthusiastic dedication to maintain the chain of distinguished CMBN leadership, to ensure and boost its success. The recent new discoveries already foretell expanded growth in 2010.

Message from the Chairman of the CMBN Board, professor Ole M. Sejersted

Ole M. Sejersted

Centre for Molecular Biology and Neuroscience (CMBN) was among the first Centres of Excellence to be established in Norway. With its multidisciplinary nature and ample competence and resources it provides unique opportunities, but also challenges in basic and translational research. CMBN has continued to grow and this annual report shows that the scientific output has been outstanding. The organizational changes in the host institution structures, both in Oslo University Hospital and the Faculty of Medicine at the University of Oslo, have not affected the activity of the Centre. The investments in heavy equipment in combination with frontline expertise has enabled CMBN also as a core facility to provide support to many scientists in neighbouring environments, way beyond the centre. I am confident that CMBN will continue to succeed scientifically and develop bridges in translational research through 2012.

Message from the Director of Research and Innovation, Oslo University Hospital, professor Erlend B. Smeland

Erlend B. Smeland

Oslo University Hospital

The vision for Oslo University Hospital (OUS) is to conduct frontline patient care, research and innovation. Excellence in science is the basis for rejuvenated and updated patient care, and we feel that the OUS is an optimal arena for translational research. More than 50 per cent of the medical research in Norwegian medical centres is performed at OUS. This is the result of the hospital's general research strategy, a close collaboration with the University of Oslo and an extensive national and international networking. In this way, OUS complies with the requirements of its owner and patients as a national reference hospital, responsible for introducing and developing new medical diagnostics, treatment and preventive measures. High quality research that supports our prioritised areas of commitment also secure the operation and development of national and multi-regional assignments. Centre for Molecular Biology and Neuroscience (CMBN) was the first Centre of Excellence at our institution and has been a major success with very favorable evaluations and high scientific output. Its multidisciplinary nature and integrated translational research contributes to OUS activities by bridging the gap between basic sciences and clinical medicine. In this context, the efforts in research related to brain disease are within the prime strategic areas selected by the hospital. It is our belief that CMBN will continue to excel and contribute to molecular medicine beyond 2009.

Message from the Head of Institute of Basic Medical Sciences, University of Oslo, professor Jan G. Bjaalie

Jan Bjålie

CMBN with its scientific vision and productive research community attests to the importance of large multidisciplinary environments. The ample competence and renewed resources provided by the centre offer unique opportunities and improved competitiveness in addressing current challenges in basic sciences. The CMBN link to Oslo University Hospital (Rikshospitalet) also represents an important link in promoting translational research.

At the Institute of Basic Medical Sciences, we are in a time of rapid scientific developments and organizational changes. In this context, CMBN investments in heavy equipment in combination with extensive training of personnel with frontline expertise are of high value for our institute, also in terms of core facilities. It is our goal to create synergies and to ensure that CMBN and other centres and networks have the host support they deserve, to ensure sustainability and continued growth. I am convinced that CMBN will continue to contribute substantially with its research and discoveries on genome instability and brain diseases.

Ole Petter Ottersen: From CMBN Director to UiO Rector

Ole Petter Ottersen

Ole Petter Ottersen was on April 2, 2009 elected as rector at the University of Oslo (UiO).

He commenced his new post on August 1, 2009 and has since then promoted UiO and science and education on various levels, including political and media venues.

Rector Ottersen on his way to work

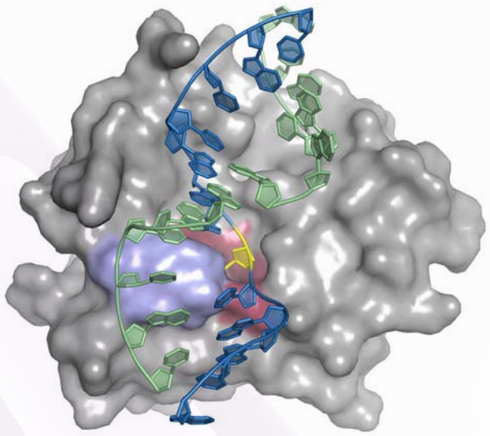
Rector Ottersen speaking to the UiO students 11th August

Photo © Fransesco Saggio

Publications high-lights 2009

Dalhus B, Arvai AS, Rosnes I, Olsen ØE, Backe PH, Alseth I, Gao H, Cao W, Tainer JA, Bjørås M.
Structures of endonuclease V with DNA reveal initiation of deaminated adenine repair
Nature Struct Mol Biol 16 (2), 138-43 2009

Bjørn Dalhus, Magnar Bjørås and co-workers published structures of the DNA repair enzyme endonuclease V in complex with DNA. Endonuclease V can initiate the repair of deaminated purine bases by recognizing them and hydrolyzing the second phosphodiester bond on their 3' side. Deamination of DNA bases, particularly via nitrosative deamination resulting from endogenous processes and increased by oxidative stress from mitochondrial dysfunction or inflammatory responses, can cause transition mutations and cancer predisposition. The endonuclease V - DNA structures provide new insight into the initial step of what has been a structurally undefined, but biologically crucial, DNA base repair pathway. The structures reveal a wedge motif acting as a minor groove damage sensor and a pocket to recognize the lesion; the enzyme remains tightly bound to the incised product, probably to hand it over to downstream repair proteins which are responsible for removal of the DNA damage and reinsertion of correct bases to restore the integrity of the DNA.



The protein surface of EndoV (gray) is optimized to bind DNA (blue and green double helix). The deaminated and damaged base (yellow) is recognized inside a specific pocket on the EndoV surface (red).

Vik A, Aas FE, Anonsen JH, Bilsborough S, Schneider A, Egge-Jacobsen W, Koomey M (2009)
Broad spectrum O-linked protein glycosylation in the human pathogen Neisseria gonorrhoeae
Proc Natl Acad Sci U S A, 106 (11), 4447-52, 2009

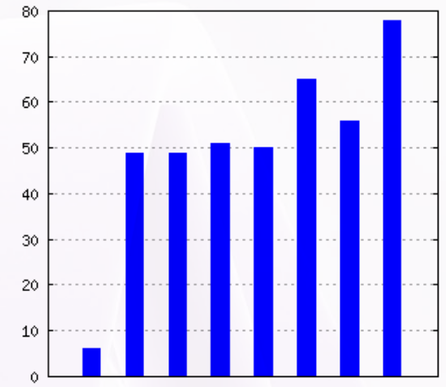
Protein glycosylation is an important element of biologic systems because of its significant effects on protein properties and functions. Koomey and co-workers identified the first general (broad spectrum) O-linked protein in bacteria in the species Neisseria gonorrhoeae, the etiologic agent of the human disease gonorrhea. By examining the 11 glycoproteins identified, it was found that, as in eukaryotes, the broad scope of this system is dictated by the relaxed specificity of the glycan transferase as well as the bulk properties and context of the protein-targeting signal rather than by a strict amino acid consensus sequence. Together, these findings reveal previously unrecognized commonalities linking O-linked protein glycosylation in distantly related life forms.

Hu H, Vervaeke K, Graham LJ, Storm JF
Complementary theta resonance filtering by two spatially segregated mechanisms in CA1 hippocampal pyramidal neurons
J Neurosci, 29 (46), 14472-83, 2009

By combining double and triple patch clamp recording from the dendrites and soma of CA1 hippocampal pyramidal neurons with computational modelling, Hu, Storm and collaborators discovered that each cell is equipped with two complementary, spatially segregated mechanisms for theta resonance filtering of synaptic input, one in the apical dendrites and the other perisomatically.

Publication record

The CMBN publication record for the years 2003 – 2009 is steadily increasing, both in actual numbers and in impact. This productivity is evidence of the healthy and multidisciplinary scientific environment that CMBN scientists enjoy.



The CMBN publication record for the years 2003 – 2009.

Organisation

Board

The Board is responsible for ensuring that CMBN develops in accordance with the current research plan and according to its statutes. The CEO and head of the CMBN board is Professor Ole M. Sejersted. Members of the board: Mari Trommald, South-Eastern Health Authoritiy, Kirsten Sandvig, Oslo University Hospital/ University of Oslo, Torgeir Bruun Wyller, Oslo University Hospital/ University of Oslo, John Torgils Vaage, Oslo University Hospital/University of Oslo, Lars Terenius, Karolinska University Hospital, Sweden. The board of CMBN will serve until the Centre of Excellence status expires in 2012.

Management

2009 has marked a change in the management of the CMBN. Professor Ole Petter Ottersen was elected Rector of the University of Oslo. As he took up this important challenge in August 2009, Professor Tone Tønjum became the Director of the Centre with overall scientific and administrative responsibilities for the Centre's activities. In her duties she is supported by Professor Jon Storm-Mathisen as Co-Director and Ms. Kristine Aa. S. Knudsen as Administrative Head. The eleven group leaders construct the Steering group of the Centre, and they meet regularly to discuss important scientific and administrative issues.

As the Centre of Excellence status is temporary, the Centre draws on the competence of the existing administrative staff at its host institutions, the Faculty of Medicine at the University of Oslo and the Oslo University Hospital (Rikshospitalet). Five of the eleven groups are located at Domus Medica of the Faculty of Medicine, UiO and five groups are located at Oslo University Hospital (Rikshospitalet). One group is located at the Faculty of Mathematics and Natural Sciences, at the Institute of Molecular Life Sciences.

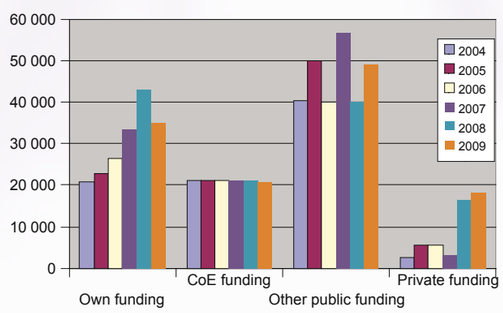
Kristine Aa. S. Knudsen
CMBN Administrative Head

Maria Beatriz Azevedo Castro da Rocha
CMBN Executive Officer

Economy

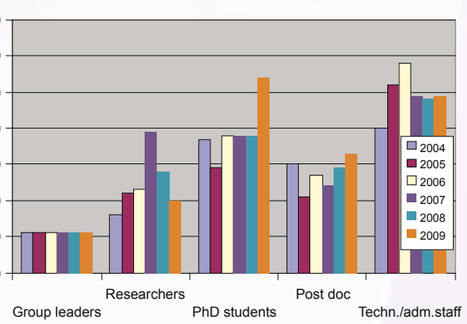
The Centre's total income was NOK 120.6 million in 2009, an increase of NOK 0.6 million from the year before. NOK 20 805 000 is the annual Centre of Excellence (CoE) grant from the Research Council of Norway. The two host institutions, the University of Oslo and Oslo University Hospital (Rikshospitalet), contribute with salaries, office and laboratory space and running expenditures of approximately 1/3 of the Centre's income while other private and public funding contributes with approximately NOK 67 million.

CMBN has throughout its time dedicated 35% of the funding from the Research Council of Norway for common infrastructure, heavy equipment with expert personnel and core facilities.



Personnel

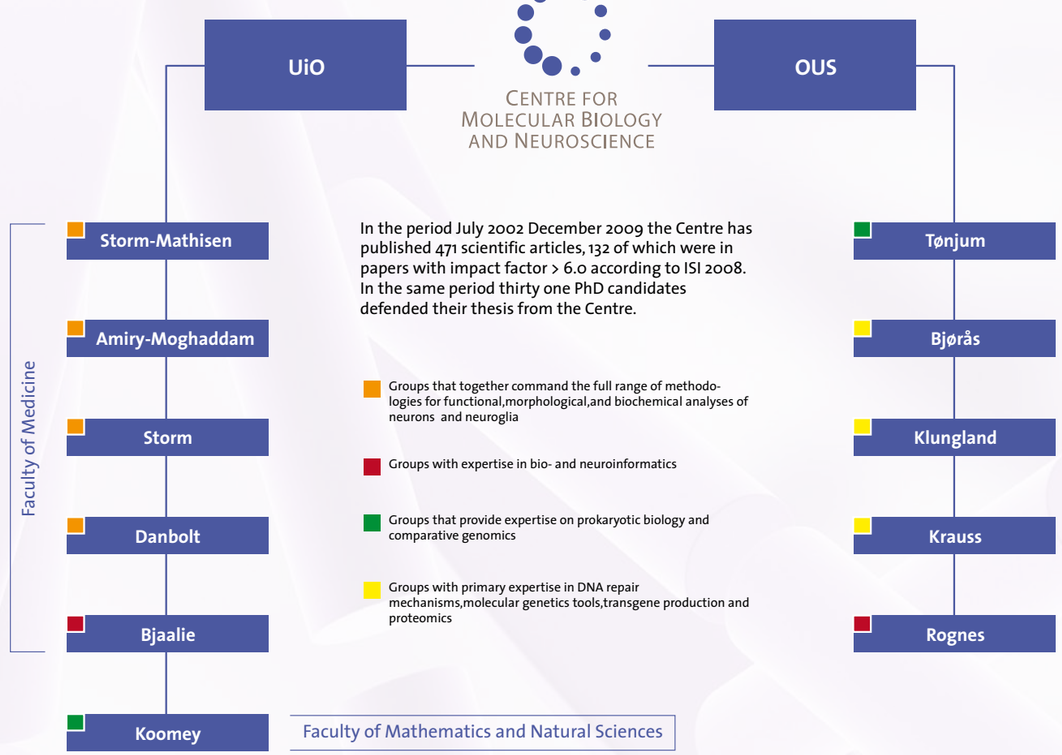
As one of the Centre's strategies is to be internationally leading within our scientific portfolio, it is of primary importance that the composition of our staff reflects this ideology. Only by conscious international networking and recruitment of staff can we secure this aim. The Centre had 38 foreign citizens from 19 different nationalities among its scientific personnel and 12 foreign citizens from 11 nations among the technical/administrative staff in 2009. Out of the nine guest researchers we hosted among the staff last year, only one was Norwegian.



Eleven groups providing the context of the Centre

The Centre consists of 11 research groups at the University of Oslo (UiO) and at the Oslo University Hospital (OUS), Rikshospitalet. The Centre activities are mainly situated in the Domus Medica and in the research building at Rikshospitalet, at Gaustad. The Groups headed by Krauss, Koomey and Rognes are located on other premises in the OUS and UiO within walking distance.

-- Through collaboration we can create more! --



In the period July 2002 December 2009 the Centre has published 471 scientific articles, 132 of which were in papers with impact factor > 6.0 according to ISI 2008. In the same period thirty one PhD candidates defended their thesis from the Centre.

- Groups that together command the full range of methodologies for functional,morphological,and biochemical analyses of neurons and neuroglia
- Groups with expertise in bio- and neuroinformatics
- Groups that provide expertise on prokaryotic biology and comparative genomics
- Groups with primary expertise in DNA repair mechanisms,molecular genetics tools,transgene production and proteomics

Genome dynamics and microbial pathogenesis

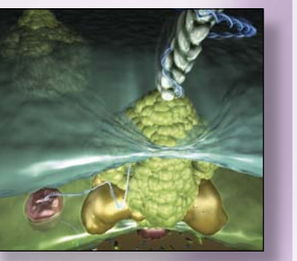
Professor
Tone Tønjum

About

The stability of microbial genomes and gene pools is constantly challenged by horisontal gene transfer and recombination, as well as DNA damage caused by endogenous and exogenous stress. Mechanisms for frequent 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 major pathogens and 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 (FEMS Microbiol Rev 2009). In this context, we have identified a number of novel DNA binding components and defined how they act and interact (Microbiol. 2009). We are also elucidating the effect of defects in DNA repair on host defence and microbial fitness and virulence in a new meningitis mouse model and the process of normal aging in a human cohort. The group addressing these challenges in molecular medicine through translational research 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. This information will enable us to develop new strategies for diagnostics, prevention and treatment of disease.



Model of the meningococcal transformation machinery based on the current information on the components involved in this process. We hypothesize that DNA enters the meningococcal cell through the large PilQ pore, which, when DNA is wound around the pilus rod, sterically just allows it to enter the cell.

Projects

- The meningococcal transformation machine: *Neisseria meningitidis* is the causative agent of meningitis, and pili are its primary virulence factor. The transport of these macromolecular structures across membranes is performed by a complex machinery, which is also coupled to transformation of DNA. We hypothesize that DNA uptake during transformation is coupled to pilus retraction (J Mol Biol 2006; J Structural Biol 2006; Microbiology 2009; FEMS Microbiol Rev 2009) and are studying the interactomics of this molecular machine.

- Search for novel signature DNA sequences: By using our combined expertise on evolutionary phylogeny, prokaryote cell physiology and comparative genomics we have defined the DNA uptake sequence (DUS) as a12-mer (J Bacteriol 2007) and are searching for signature “dialects”.

- 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).

- Genome maintenance in *Mycobacterium tuberculosis*: We are studying the impact of helicases in genome maintenance and thereby fitness for survival in the world’s biggest bacterial killer (PloSOne, 2008; FEMS Microbiol Rev 2009).

- The “fountain of youth”: The effects of the DNA repair SNP profile in the process of normal aging is addressed in a human cohort.

Recent achievements: Identification of novel DNA binding components (Microbiol. 2009), antimutator role of bacterial MutY, MutS and Fpg (Nature Micro. Rev. 2006, BMC Microbiol 2009, FEMS Microbiol Immunol 2009), the true identity of the neisserial DNA uptake sequence (J Bacteriol 2007), defining transformation as a conservative process maintaining genome stability (Genome Biology 2008, FEMS Microbiology Rev 2009), genetic predisposition for disease (CID 2008, FEMS Microbiology Rev 2009)

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Synaptic neurochemistry laboratory

Professor
Jon Storm-Mathisen

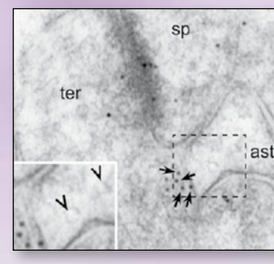
Associate Professor
Linda H. Bergersen

About

The group’s main interests are the mechanisms underlying synaptic transmission and gliotransmission, and the role of metabolism and energy supply for the function of gray and white matter. 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 astrocytes 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.



Glutamate from astrocytes stimulates nerve endings in hippocampus. Electron micrograph showing NMDA type glutamate receptor subunits NR2B (immunogold particles) at the synapse as well as in extrasynaptic membranes (arrows) of nerve terminals (ter) that synapse on dendritic spines (sp). NR2Bs face astrocytic processes (ast) containing glutamate laden synaptic-like microvesicles (arrowheads in enlarged inset). Scale bars, 100 nm. blank” Nature Neuroscience (doi:10.1038/nn1849)

Projects

- Identification of gliotransmitters and their roles in neuron-glia communication.

- 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 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, as well as in experimental models of heart failures and epilepsy.

- Synaptic changes during ontogeny and deficient DNA repair.

Recent achievements: Findings that astrocytes store and release neurotransmitter amino acids in a way resembling synaptic release (Nature Neurosci 2004, 2007, Neuroscience 2009a), that glutamate mediates retrograde signaling from dendrites (Cereb Cortex 2009a) and that glutamate and other neuroactive substances can be co-released from nerve endings (Cereb Cortex 2009b) imply novel ways of intercellular communication and potential drug targets. Observations in synapsin knock-out mice that develop epilepsy (Cereb Cortex 2009c) and in a rat model of ADHD (Neuroscience 2009b) implicate anomalous glutamate signalling in these diseases. Ionotrophic glutamate receptors are involved in nociception (Mol Neurobiol 2009), can cause hypoxic damage in myelin (Nature 2005) and mediate signals that position mitochondria where they are most needed, i.e. at the postsynaptic site of active synapses (Neuron 2009). Inducible expression of a mutated mitochondrial UNG1 DNA repair enzyme in forebrain neurons caused generation of apyrimidinic mDNA and neuronal impairment including reduced size of synaptic contacts (Mol Cell Mol 2010). Eccentric muscle actions cause ultrastructural changes in human subjects (J Appl Physiol 2009 a, b). Increased MCT1 expression after ischemia and reperfusion restore cardiac pH through lactate export (Life Sci 2009). Review of the literature underlines a role for vesicular release of glutamate from astrocytes in synaptic transmission (Neuroscience 2009a). Symposia were published, on the glutamate synapse (Neuroscience 2009c), and on synaptic plasticity and memory (Neuroscience 2009d).

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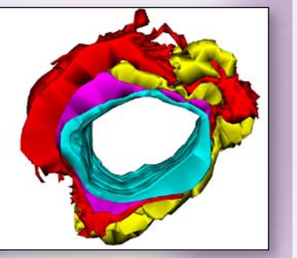
Laboratory of molecular neuroscience

Associate Professor
Mahmood Reza
Amiry-Moghaddam

About

The Laboratory for molecular neuroscience involved molecular mechanismsinvolved in the development of acute and chronic neurodegenerative diseases. It aims at unraveling the molecular basis for cell death and edema development in stroke and other neurological conditions, and explores the pathophysiology of Alzheimer's disease, Parkinson's disease and temporal lobe epilepsy. Long time goals are to identify new molecular targets for neuroprotective strategies in stroke, and other conditions involving glutamate excitotoxicity, and to develop novel approaches for the treatment of brain edema.



3D- reconstruction of amyloid around a brain microvessel in a mouse model of Alzheimer disease. The amyloid (red) is in the extracellular space around the astrocyte-endfeet-endothelial complex. The amyloid touch several structures of the complex (pericyte (magenta), astrocyte endfoot (gold) and endothelial cell (blue). From a project together with Paworn Nuntagij and Reidun Torp

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, Parkinson'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.
- Synthesis of small molecule blockers of the brain aquaporins and assessing their effect on development of brain edema
- Exploration of the composition and function of the extracellular matrix protein complexes that interact with the membrane proteins
- Unraveling novel drug targets and therapeutic strategies in Parkinson's disease
- Exploration of mechanisms involved in the formation of beta-amyloid in aging andAlzheimer's disease

Recent achievements: 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). Exploring the role of matrix metalloproteinases in epileptogenesis (J Cell Biol 180: 1021 - 35, 2008). Recording volume changes in individual neurons of the intact brain by multiphoton microscopy (Glia 56:895-902, 2008). 3D reconstruction of amyloid deposits in mouse modell of Alzheimer's disease (J Alzheimers Dis. 2009 Feb;16(2):315-23)

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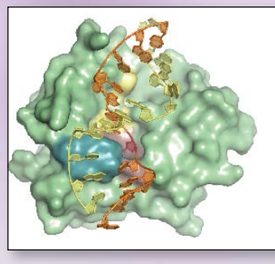
Laboratory for molecular biology

Professor
Magnar Bjørås

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 EndoV DNA damage (hypoxanthine) recognition complex (Dalhus et al).

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, stem cell maintenance and neurological disease.

Projects

- Role of DNA base lesion repair in ageing, cancer and neurological disease.
- Biogenesis and maintenance of mitochondrial DNA.
- Model studies of DNA damage responses and ageing in yeast.
- Small RNA genes and small peptides 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/progenitor cells.
- Structural biochemistry of base lesion repair.

Recent achievments: An experimental model of heart failure in rat showed up-regulation of myocardial DNA Base Excision Repair activities (Mutation Research . 666, 32-38 (2009)). The 3D atomic structure of Endonuclease V in complex with DNA was solved and reveals the structural basis of repair of deaminated adenine in DNA (Nature Struct. Mol. Biol., 16, 138-43 (2009)). Identified catalytically impaired hMYH and NEIL1 mutant proteins in patients with primary sclerosing cholangitis and cholangiocarcinoma (Carcinogenesis . , 1147-54 (2009)). modulation of DNA glycosylase activities during cultivation of human mesenchymal stem cells (Exp. Cell Res. 315, 2558-67 (2009)). CSB defective cells showed accumulation of mitochondrial DNA damage and bioenergetic dysfunction (FEBS J. 2009 May;276(10):2811-21). Characterized expression patterns of *Neil3* during embryonic brain development and neoplasia (BMC Neurosci, 10, 45 (2009)). The Saccharomyces cerevisiae Rad6 postreplication repair and Siz1/Srs2 homologous recombination-inhibiting pathways process DNA damage that arises in asf1 mutants. (Mol Cell Biol. 2009 Oct;29(19):5226-37).

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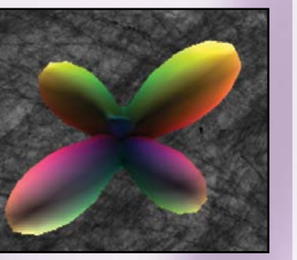
Laboratory of neural systems and graphics computing

Professor
Jan G. Bjålie

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 *Professor* atlasing.



Validation of the accuracy of diffusion MRI for measuring complex neural fibre orientations in the brain, providing a basis for development of new analytical tools in basic and clinical research.

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 structurefunction relationships are often better understood by introducing 3-D reconstruction and advanced visualization and modelling tools.

Projects

- *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.

- *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.

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

- *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) Publication of a benchmark histological validation of advanced diffusion magnetic resonance imaging (MRI) approaches for measuring complex tissue orientations in the brain, with implications for basic research and clinical applications (Leergaard et al., PLoS One, in press). 2) Establishment of an online atlas application for dissemination of high-resolution microscopic images showing neurotransporter distributions in the entire brain (Holmseth et al., 162:1055-1071, 2009, collaboration with the CMBN-Danbolt group). 3) Continued expansion of The Rodent Brain WorkBench (www.rbwb.org) with tools and database. 4) Demonstration of novel digital brain atlasing applications (with focus on brain connectivity and whole brain molecular distribution patterns) at international conferences, preparing for future release via the The Rodent Brain WorkBench.

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Neurotransporter group

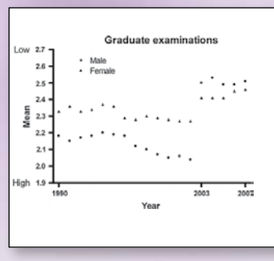
Professor
Niels Chr. Danbolt

About

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

Challenges

The human genome contains almost 400 different transporter protein genes, most of which are expressed in the nervous system. The encoded proteins, including those for glutamate, are subject to sophisticated dynamic regulation, and several of them are doing more than solute transport. They are also ion channels and take part in intracellular signalling. Thus, the transporters are not simply pumps, but these other 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 as disturbed control of extracellular glutamate appears to be an important factor, directly or indirectly, in all neurological disorders (including traumatic injury, epilepsy and stroke) as well as in drug abuse and major psychiatric disorders (for review see: Danbolt, 2001: Prog. Neurobiol).



In Norway, the Quality Reform in 2003 was the first step on implementing the Bologna Process which aims to develop a coherent and compatible higher educational system in Europe. We have analyzed data on grades (495,334 examinations) from the UiO (1990 - 2007) to see if the reform affects male and female students differently, and show that females benefit more than males from the system change (see figure; Lehre et al., 2009a). We also show that males are more variable than females, not only with respect to intelligence, but also with respect to other parameters such as birth weights, physical performance, adult weight, height, and blood composition. This suggests that higher variability among males constitutes a fundamental sex difference (Lehre et al., 2009b).

Projects

- Conditional deletion of transporter genes (GAT2, GAT3, BGT1 and EAAT2) and of the gene for glutamine synthetase (GS).
- The role of the GABA transporters in seizure control.
- The importance of EAAT2 in nerve terminals
- Brain ultrastructure: 3D-models of neuropil and of blood vessels
- Determination of GABA and glutamate transporter distributions and densities around select synapses.
- Computer modelling of transmitter release, diffusion, removal and receptor activation.
- The roles of transporters in peripheral organs (endocrine pancreas, heart, kidney and liver).
- Mechanisms behind gender differences in variability
- Laboratory automation: “What a robot can do, a robot should do.”
- Development of systems for data handling and authentication, as well as for sample tracking and data exchange between researchers.

Recent achievements: The neurotransmitter glutamate is inactivated by cellular uptake; mostly catalyzed by the glutamate transporter GLT1 (slc1a2, excitatory amino acid transporter [EAAT2]) subtype which is expressed at high levels in brain astrocytes and at lower levels in neurons. Three C terminal variants of GLT1 exist (GLT1a, GLT1b and GLT1c). Their cellular distributions are currently being debated (that of GLT1b in particular). We have made antibodies to the variants and produced pure preparations of the individual variant proteins in order to quantify the levels of each variant protein (Holmseth et al., 2009) and conclude that GLT1a represents most of the total GLT1 protein in the normal young adult rat forebrain, and this variant is the one with is expressed by synaptic terminals. At 8 weeks of age, the levels of GLT1b and GLT1c are, respectively, 15 times and two orders of magnitude lower. Both GLT1a and GLT1b are expressed in astroglia and both proteins are found both in astrocytic cell bodies and in the smallest ramifications of the astrocytes close to synapses and those surrounding blood vessels. The relationship between the concentrations of the variants changes between brain regions and during development suggesting that these proteins are differentially regulated.

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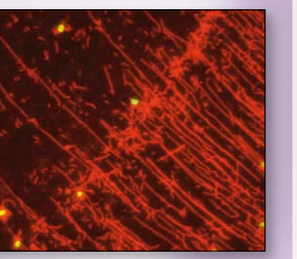
Molecular and cellular basis of microbial pathogenesis

Professor
Michael Koomey

About

Our laboratory uses human associated species of the bacterial genus Neisseria to address fundamental questions as to how bacterial pathogens cause disease in man. The research has focused primarily on the structure - function relationships of bacterial surface proteins. Recently, we have extended these studies to include investigations of covalent post-translational modifications (PTM) of surface proteins. These efforts have focused primarily on these processes in two, closely related species of causing disease in man: *N. gonorrhoeae* (causing gonorrhea) and *N. meningitidis* (the etiologic agent of epidemic meningitis). In particular, we are harnessing knowledge to understand what factors might dictate the propensity for *N. meningitidis* to colonize the nasopharynx and occasionally cause meningitis while *N. gonorrhoeae* resides at genital sites. This work is supplemented by studies of *N. lactamica*, a third closely related species that harmlessly colonizes the nasopharynx.



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

Challenges

Despite the rapid acquisition of bacterial genome sequences, attempts at inferring phenotype from genotype remain difficult tasks. Moreover, covalent PTMs of proteins provide unique sources for structural complexity and diversification and by modifying structure and potentially function, they are likely to play an important role in the parasite-host interaction. We use research strategies combining biochemistry, bioinformatics, and reverse genetics together with advanced mass spectrometric-based proteomic approaches to examine PTM status. Challenges are to understand the basic biology of bacterial surface molecules, identify the components involved in modifying their structure, and to understand the biological significance of PTMs in these model systems. A long term goal is to understand the evolution and phylogenetic distribution of PTM systems in bacteria. Several collaborations, internationally and within the Centre for Molecular Biology and Neuroscience, have been initiated.

Projects

- Diversity of protein-associated glycan forms in Neisseria
- Genetic basis of protein-associated glycan diversification in Neisseria
- Effects of protein glycosylation on protein structure and function
- Dynamic interplay between glycosylation and zwitterionic phospho-from modifications
- Roles of glycoproteins in terminal respiratory pathways (oxygen targeting and denitrification)

Recent achievements: Unique modifications with phosphocholine and phosphoethanolamine define alternate antigenic forms of *Neisseria gonorrhoeae type* IV pili (Hegge et al, 2004); *Neisseria gonorrhoeae O*-linked pilin glycosylation: functional analyses define both the biosynthetic pathway and glycan structure (Aas et al, 2007); genetic and functional analyses of PptA, a protein targeting, phospho-form transferase (Næssen et al, 2008), and discovery of the first general (broad spectrum) *O*-linked protein glycosylation in bacteria (Vik et al, 2009).

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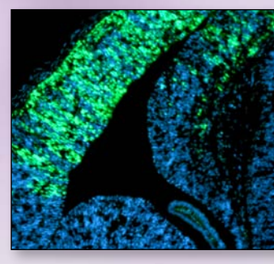
Forebrain development and neural stem cells
Stem cell pathways

Professor
Stefan Krauss

About

Stem cell knowledge is of fundamental importance, both within regenerative medicine, and in tumour medicine. Stem cells are defined as cells which are able to both extensively self-renew and differentiate into progenitors. Stem cells are controlled by signals that direct the choice between different stages. Unsurprisingly, the same signals that control stem cells, also play a central role in tumour growth and maintenance. The main interest of the group is to analyze the implications of stem cell pathways in developmental models, stem cells and cancer. The central focus is on canonical Wnt signaling and on Hh signaling. Having discovered the key morphogen Shh in 1993, the laboratory has continued to contribute to the understanding of Hh and Wnt signaling in the neural system. Recently, the laboratory has expanded into using pharmacological approaches to further understand the ramifications of the two pathways and possibilities for in vivo intervention with their activity.



Activation of the canonical Wnt signaling in the developing mouse cortex by beta-catenin-Lef1 fusion protein in D6-CLEF transgenic mice (green: beta-catenin-Lef1 protein; blue: DAPI). Ondrej Machon

Challenges

A detailed analysis of the mechanisms that control stem cell pathway maintenance, induction and inhibition are essential for understanding development and cancer. Using a combination of inducible transgenic models, siRNA and reverse proteomics we identify functionally relevant key steps in Wnt and Hh signaling that can be used for therapeutic intervention.

Projects

- Elucidating the roles of canonical Wnt signaling at different stages of forebrain development
- Analyzing the interplay between stemcell pathways and oxysterol metabolism
- Analyzing drugable targets in the Hh and Wnt signaling pathway
- Developing Wnt agonists for neurogenerative conditions

Recent achievements: Using transgenic models we have mapped the role of canonical Wnt signaling in cortical development. We have shown that in the pre-neurogenic stage, canonical Wnt signaling is essential for area specification and expansion. We have then demonstrated that canonical Wnt signaling is blocked to enable a shift between the pre-neurogenic and neurogenic program. This process is driven by a morphogenetic gradient that expands from the anterior-lateral cortical edges. In areas with continuously high levels of canonical Wnt signaling, hippocampal and DG fates are specified. Abrogation of canonical Wnt signaling in the area of the presumptive dentate gyrus leads to a significant depletion of the premigratory DG progenitor pool.

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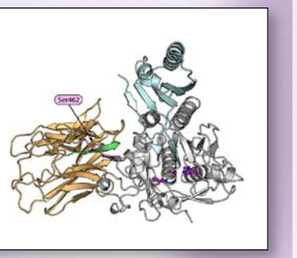
Bioinformatics group

Associate Professor Torbjørn Rognes

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 structure, 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.



Structural model of the PCSK9 protein that mediates degradation of the low density lipoprotein (LDL) receptors. The important Ser462 residue that reduces secretion when mutated is indicated. From Cameron et al. 2009.

Challenges

Huge amounts of molecular biology data is being generated from a range of different technologies. New technologies allows extensive sequencing to be carried out to analyse transcription, sequence variation, epigenetics and other phenomena. Complete genome sequences from more than a thousand organisms as well as data from large-scale protein structure determination projects is also publicly available. The main challenge in computational biology is to integrate and make sense of all of this data.

Projects

Structural bioinformatics: Computational models of the 3D structure of proteins are created and studied in order to understand the molecular mechanisms of enzyme activities. How does mutations affect the structure and function of a protein? Docking and molecular dynamics simulations are also used in our studies.

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.

Transcription analysis: Custom microarrays have been designed to study transcription in bacteria and humans. Tiling arrays are used to identify novel transcribed regions in intergenic regions of bacterial genomes. Custom arrays have also been designed to identify human oncogenic fusion transcripts. Large scale sequencing are now used to analyse transcriptional patterns.

Genome analysis: Human and bacterial genome sequences are analysed to identify particular patterns and frequent sequences, as well as variation in the sequences at particular positions. **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).

Recent achievements: Characterized mutations in the PCSK9 gene involved in cholesterol metabolism (J Int Med 2008, Atherosclerosis 2009) and analysed conservation of the gene (FEBS J 2008). Developed methods for design and analysis of custom tiling microarrays (PLoS One 2009) and arrays for detection of oncogenic fusion transcripts (Mol Cancer 2009). Analysed the mutational spectrum in human segmental duplications (BMC Genomics 2009) and sequences in human G-quadruplex motifs (Nucleic Acids Res 2009).

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Laboratory for genome repair and regulation

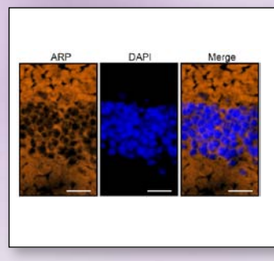
Professor Arne Klungland

About

The Laboratory for genome repair and regulation studies individual genes and their roles in basic biological processes including DNA repair, post translational regulation and epigenetics. We focus on the in vivo roles of such genes and therefore generate model organisms carrying defined mutations.

Challenges

Our research focuses on the identification of novel genes with roles in genome repair and regulation. To address this we generate single mutants in mice. Subsequent analysis aim at identifying biological roles, such as cancer, premature ageing and neurodegeneration associated with null mutagenesis of a single gene. We are particularly interested in defining the precise molecular role of individual genes in vivo. Although a protein might be able to carry out a specific reaction in vitro, the exact localization of the protein in vivo, the requirement of specific partners, the regulation of the protein during embryo development, etc, are key regulators for the activity of the protein in vivo. Such factors can even completely change the substrate preference. Today we focus on defining roles for a novel class of hydroxylases (which in vitro has been shown to hydroxylate/demethylate DNA, tRNA and histones) in epigenetic reprogramming in pluripotent stem cells and during spermatogenesis.



Mitochondrial DNA Toxicity in Forebrain Neurons causes Apoptosis, Neurodegeneration and Impaired Behavior. The panels shown (from Lauritzen et al MCB, 2010) illustrate AP-site appearances in mutUNG1-expressing mice. Coronal cryosections of the hippocampus and cerebellum probed with an aldehyde-reactive probe and stained with DAPI demonstrate a high level of AP-sites, but only in the hippocampus of induced mutUNG1 mice. AP-sites are only seen in parts of the hippocampus containing mitochondria, not nuclei, here demonstrated in a mutUNG1 mouse induced for 3 months. Scale bar=25 µm. Scale bar=100 µm.

Projects

- Role of FEN1 in DNA repair and replication with focus on cancer development
- Modelling triplet expansion in Huntington disease mice.
- Role of Alkbh1-8 in DNA repair, epigenetic regulation and tRNA modifications
- Stem cells; pluripotency and lineage commitment.

Recent achievements: We have succeeded in generating null-mutant mice for all 8 Alkb homolog's (Alkbh1-Alkbh8) and are currently characterizing these models. Whereas some homolog's have specificity for DNA repair (EMBO J 2006) others have roles in epigenetic reprogramming (unpublished), and one homolog, which is characterized in collaboration with the Falnes group, has unique specificity for the uridine in the wobble position of certain tRNA's (MCB 2010). In collaboration with Falnes we have also described four distinct groups of AlkB DNA-dioxygenases in bacteria (NAR 2009).

Another mouse model has allowed us to target DNA damage specifically to the mitochondria of forebrain neurons and to follow the biological impact of this mitochondrial DNA damage (MCB 2010)

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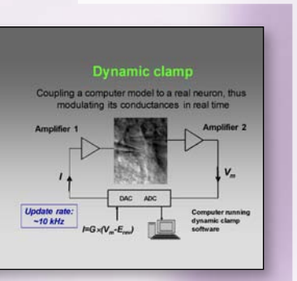
Laboratory of cellular neurophysiology and ion channel function

Professor
Johan F. Storm

About

Our group is interested in mechanisms of brain function, from molecules to behaviour. We study fundamental principles and mechanisms of neuronal signalling in the mammalian brain, in particular the roles of ion channels in cortical neurons and circuits, mainly in the hippocampal-entorhinal memory system and the neocortex.

Methods: Electrophysiological and optical recordings (patch clamp, intracellular recording, dynamic clamp, calcium imaging, flash photolysis) in brain slices and in vivo, molecular genetic (viral vectors and transgenic mice) and pharmacological manipulations, computational modelling (Neuron, SurfHippo), and behavioural tests (water maze etc.).



Dynamic clamp: a live hippocampal pyramidal neurone in a rat brain slice is coupled, via two patch pipettes, to a computational model, thus modulating intrinsic ionic currents (Hu, Vervaeke & Storm, unpublished).

Challenges

To determine the functional roles and interplay of multiple signalling mechanisms and ion channel types within different neuronal compartments, within each neuron, and in small neuronal circuits.

To elucidate functional roles of specific neuronal populations, signalling mechanisms and ion channel types, in active neuronal networks, and in the brain of behaving animals.

To elucidate the roles of neuronal signalling mechanisms in ageing and neurological disease, including ischemia/stoke, neurodegenerative disorders, epilepsy, and memory disorders.

Projects

- The roles of Kv7/KCNQ/M, h/HCN and other ion channels in neuronal signalling, brain oscillations and electrical resonance, synaptic plasticity, cognitive functions and epilepsy.
- The roles of Ca2+-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 development and ageing.

Recent achievements: By combining double and triple patch clamp recording from the dendrites and soma of CA1 hippocampal pyramidal neurons with computational modelling, we recently found that each cell is equipped with two complementary, spatially segregated mechanisms for theta resonance filtering of synaptic input, one in the apical dendrites and the other perisomatic (Hu et al., J. Neurosci. 2009). Walter Kaufmann et al. (J.Comp.Neurol, 2009), found that large-conductance calcium-activated potassium (BK) channels in Purkinje cell plasma membranes are clustered at sites of hypolemmal microdomains. In collaboration with Peter Ruth's group we found that BK-type Ca2+-activated K+ channels mediate neuroprotection and enhance survival after cerebrovascular stroke. We found that SK (KCa2) channels do not control somatic excitability in CA1 pyramidal neurons but can be activated by dendritic excitatory synapses and regulate their impact. (Gu et al. J. Neurophysiol. 2008). We have also discovered that BK-type Ca2+-activated K+ channels can enhance early high-frequency firing and mediate a novel form of spike frequency adaptation (Gu et al., J Physiol 2007). 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 Neurophysiol, 2008; 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), and that KCa1/BK-type K+ channels are essential for cerebellar learning and motor control (Proc Natl Acad Sci USA 101: 0474-8, 2004).

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Core facilities at CMBN

CMBN has throughout its time dedicated 35% of the funding from the Research Council of Norway for common infrastructure and heavy equipment. Along with the large equipment, expert personnel has been employed to facilitate maximal quality, efficiency and out-put. Thereby, CMBN has contributed to the establishment of a range of core facilities in its host institutions, serving scientists in CMBN and beyond.

Enlisted are some examples of the core equipment that have facilitated CMBN scientific breakthroughs and networking

DNA sequencing

Mass spectrometry (5,6)

Structural biology/ X-ray crystallography (2,3)

Thyphoon Imaging

Confocal microscopy (1)

Electron microscopy

Two/Multi Photon microscopy

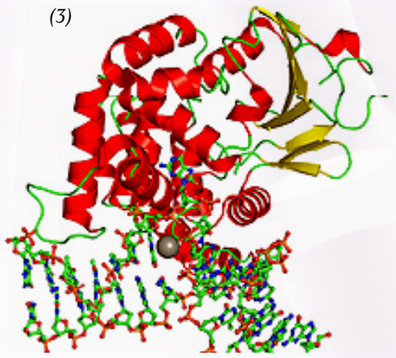
High throughput tissue processing

Neuro/bioinformatics

Transgene technology (4)


(1)

(2)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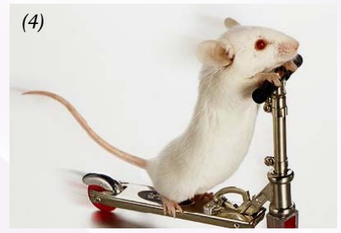
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PhD degrees 2009

Gunn A. Hildrestrand
Intracellular localization and expression patterns of DNA glycosylases and their activities in murine and human stem cells
Faculty of Medicine, University of Oslo
18 June 2009
Supervisors: Luisa Luna and Magnar Bjørås

Jan Gunnar Sørbø
Analysis of AQP4 gene and gene expression in rats: RNAi targeting and identification of novel isoforms
Faculty of Medicine, University of Oslo
23 September 2009
Supervisors: Torgeir Holen and Ole Petter Ottersen

Emma Lång
Meningococcal inner membrane proteins and their role in transformation
Faculty of Medicine, University of Oslo
20 November 2009
Supervisor: Tone Tønjum

Investment for the future: Support for young scientists

An important part of the common investments was dedicated as support for young and promising scientists.

This support is meant to provide salary while recruiting individual funding and generate a basis for the development of independent research groups. The scientists are also offered practical support, advice and infrastructure.

The CMBN scientists receiving this support must on a competitive basis apply for further financing from national and international funding agencies.

Scientists supported in 2009

Ole Herman Ambur

Genome evolution and genetic transformation in bacterial sex

Linda Hildegaard Bergersen

Role of glutamate and lactate in synaptic transmission

Bjørn Dalhus

3D Structural biology of DNA repair components and structure based drug design

Letten Research Centre (LRC)

LRC is a facility for *in ivo* brain imaging at the Institute for Basic Medical Science/Centre for Molecular Biology and Neuroscience. A generous donation from Letten Foundation made it possible to establish the centre. LRC will accommodate two state-of-the-art setups for multiphoton laser scanning microscopy equipped with two independent lasers and electrophysiology rigs. The equipment will be used to study brain development as well as causes and treatments of neurological and psychiatric disease.

Opening of LRC in May 2009 (Photo: Gunnar F. Lothe)

CMBN scientist awarded group leader position in Molecular Medicine

Erlend A. Nagelhus, MD, PhD, received in 2009 a 16 MNOK Group Leader grant (5 years, renewable) from the Centre for Molecular Medicine Norway, the Nordic EMBL partnership, University of Oslo (www.ncmm.uio.no).

Nagelhus will run his research group GliaLab at the Institute of Basic Medical Sciences, in affiliation with CMBN, and be responsible for the neuroimaging activity in Letten Research Centre. GliaLab will use *in vivo* two-photon imaging to explore roles of aquaporins and associated glial molecules in synaptic activity and signaling at the brain-vascular interfaces. The goal is to provide novel strategies for treatment of neurological disorders with perturbed neuronal function and circulation.

YFF

Identification of novel CDK-regulated processes and targets. Dr. Jorrit Enserink works at the Institute of Microbiology at the Oslo University Hospital, Oslo, Norway.

Jorrit Enserink

Research in the Enserink lab focuses on regulation of the cell cycle. Progression through the cell cycle is orchestrated by cyclin dependent kinases (CDKs). The importance of cell cycle and CDK research is underscored by the fact that aberrant CDK activity underpins the growth of all human tumors. While the upstream regulation of CDKs is quite well understood, remarkably few downstream CDK targets have been identified. A thorough understanding of the CDK-controlled targets and processes is important, because it may open new avenues for development of chemotherapeutic drugs. The goal of this research is to identify novel processes and substrates controlled by CDKs. For these studies, we make use of a model organism, budding yeast, because cell cycle control has remained essentially unchanged during evolution. Making use of powerful yeast genetics, we have started to unravel the genetic network of the cell cycle, and discovered several novel CDK-controlled processes

Dr. Jorrit Enserink was awarded YFF (Yngre fremragende forskere) funding through the Research Council of Norway for the project “The Function of Cyclin Dependent Kinases in the DNA Damage Response and Maintenance of Genome Stability”. The purpose of the YFF-program is to provide young talented researchers with a level of research funding that will allow them to reach an international top level. Dr. Enserink was one of 20 to be funded among 179 applicants across all fields of research in Norway.

Achievements in 2009

Medinnova prize - Anti-microbial peptides: James Booth, Ragnhild Weel-Sneve, Knut Kristiansen og Magnar Bjørås

Patents: Antibacterial polypeptides and use thereof – patent Application No.: 09172106.8, date of filing: 2 October 2009, Applicant(s): Oslo Universitetssykehus HF, Inventor(s): Magnar Bjørås, Knut Ivan Kristiansen, Ragnhild Weel-Sneve, James Booth

Educational activities

All CMBN Educational activities collectively make up the CMBN Research School.

PhD school: All courses contribute to the education PhD and other student groups, enabling qualified study points in the UiO doctorate programme.

Advanced Neuroimaging Workshop

CMBN, Centre for Molecular Medicine Norway, FUGE, and Institute of Basic Medical Sciences arranged a neuroimaging workshop in December 2009. Topics included in vivo two-photon laser scanning microscopy, quantitative immunogold electron microscopy and digital brain atlasing. The workshop covered basic concepts as well as hands on training. Lectures on career planning were also featured.

Translational research at the European level: In the context of the ESFRI initiative EATRIS (European Advanced Translational Research InfraStructure in Medicine), CMBN is contributing to shaping education in science at the European level. EATRIS is planned to be a distributed pan-European infrastructure consisting of a network of biomedical translation research centres across Europe.

Conferences and seminars

Nordic Centre of Excellence / Nordic network: WIRED Together with laboratories at Karolinska Institutt, Panum institute and University of Århus, the CMBN has been member of WIRED. In June 2009, the centre organized an international symposium with 128 participants. The centre expired end 2009 but the research groups will continue their collaboration in the future.

Advances in Molecular Mechanisms of Disease - High Throughput Platforms and Advances in Imaging. Courses and symposia organized in co-operation with Nordic Centre of Excellence in Molecular Medicine, and Scan Balt, Oslo, June 2009

2nd Erling Seeberg seminar: Symposium on DNA repair, in Ålesund/Geiranger, June 2009

Transatlantic Science Week September, 2009, Minneapolis: Discover – Innovate - Collaborate. **Satelite Event:** Neuroscience Symposium, Neuron-Glia Interactions - From Perisynaptic To Perivascular Communication. Speakers and organizers from the University of Minnesota and the University of Oslo

Oslo Transgenic meeting, Lysebu, September 2009 and **Norwegian Stem Cell Networking** Meeting 2009, 7-8 October 2009

Neurodegeneration and Aging Seminar: CMBN guest professor and UiO honorary doctor Vilhelm A. Bohr, Maria Rossi and Lene Juehl Rasmussen, December 2009

CMBN gender equality seminar: How to make women become leaders in academia, Rikshospitalet

CMBN Fall seminar: Building bridges between clinical medicine and basic science

Networking

Oslo Neuroscience Network (ONN)

The goal of the ONN is to promote translational research in brain disease. Vidar Gundersen, CMBN, Institute of Basic Medical Sciences, and Department of Neurology, Rikshospitalet, was elected as head of ONN in July 2009. ONN is an expansion of Gaustad Neuroscience Network to comprise all neuroscience communities in the Oslo region.

The Norwegian Brain Council (Hjernerådet)

www.hjerneradet.no

The Norwegian Brain Council (NBC, www.hjerneradet.no) was established in 2007 to promote knowledge on brain diseases in the society and represent links between patient organizations, the neuroscience community, health authorities and politicians. CMBN director Tone Tønjum has been instrumental in founding NBC and working in the executive board. NBC is a member of the European Brain Council.

The Nansen Neuroscience Network (NNN) is emerging

- Working Hard for a Healthy Brain -

Based on the long tradition of first class neuroscience research and innovative ideas leading to commercial initiatives, CMBN has in collaboration with MI-lab in Trondheim, supported by several other academic and industrial groups in Norway, taken the initiative to form the Nansen Neuroscience Network (NNN).

This national innovation cluster – or rather a knowledge transfer network – in neuroscience, includes basic and clinical research environments, as well as relevant industrial partners. NNN initiative will promote innovation for the "Healthy Brain", and help remove the "translational block" by ensuring that discoveries in basic neuroscience be converted into improved prevention, diagnosis and therapy. NNN is also meant to increase the awareness of unmet needs in clinical practice. Innovation Norway (IN) represented by Ole Jørgen Marvik and the local IN office in Oslo has been most supportive in our endeavours to build improved alliances with industry and regional and national research institutions, and we also feel that there is a political backing for the NNN initiative.

NNN Project leader Stein Lorentzen-Lund

The name of the knowledge transfer network is inspired by the explorer, humanitarian and diplomat, Fritjof Nansen, also a prominent neuroscientist, who pioneered routes to the mind and new frontiers. About 122 years ago, Nansen earned the first Norwegian doctorate degree in neuroscience, demonstrating that the brain consists of individual, separate nerve cells. Since then, Norwegian scientists have given a number of seminal contributions to our knowledge about the brain, establishing neuroscience as a field of excellence in Norwegian science..

Our vision:

NNN will be a driving force in connecting brain *science and industry*

NNN aims at creating smart solutions for individuals and society

NNN is committed to improving quality of life through innovation, research and development of diagnostics, therapeutics and preventive measures

The Kavli Prize in Neuroscience

CMBN Co-Director Jon Storm-Mathisen serves as Chairman of the Kavli Prize Committee on Neuroscience, which as of 2009 consists of the following other members, appointed by the Norwegian Academy of Science and Letters (DNVA) among outstanding neuroscientist named by sister academies in Europe and the USA: Tobias Bonhoeffer, Jean-Pierre Changeux, Eric Kandel, and Charles F. Stevens.

The *Kavli Prize* (www.kavliprize.no), awarded for the first time in Oslo on September 9th 2008, is a joint venture by the DNVA, the Norwegian Ministry of Education and Research, and the Kavli Foundation (based in California). A prize of USD 1,000,000 is given biannually in each of the three fields, astrophysics, nanoscience and neuroscience, to recognize the most significant basic research in the fields that the donator Fred Kavli foresees will bring the most magnificent future progress but which are not sufficiently emphasized by the Nobel Prize.

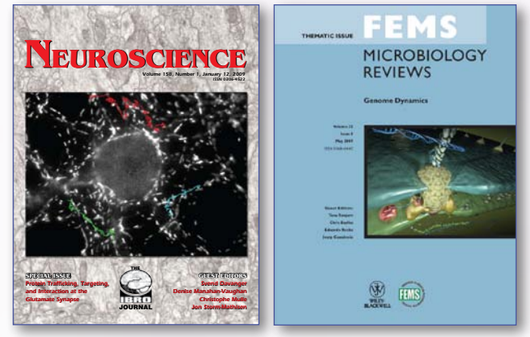
The inaugural prize winners Sten Grillner, Thomas Jessell, and Pasko Rakic, who received the prize *"for discoveries on the developmental and functional logic of neuronal circuits"*, were interviewed in *Nature Reviews Neuroscience* 9(12):893-7. A review of the work of the prize winners (by JC Glover) and a synopsis of the Kavli Prize Inaugural Symposium on Neuroscience (by M Sander, LH Bergersen, J Storm-Mathisen) were published back-to-back as the first papers in an issue of *Neuroscience* 163(4):965-984, 2009 with an illustration from the Symposium on the cover.

In 2009, the *selection process* for the prize 2010 was initiated, involving nominations from scientists worldwide (expiring 15th December 2009).

Editorial activities

CMBN Director Tone Tønjum served as Guest Editor for the Thematic Issue on "Genome Dynamics" in *FEMS Microbiology Reviews* 33(3) May 2009.

Svend Davanger, Ole Petter Ottersen and Jon Storm-Mathisen served as Guest Editors for the Special Issue on "Protein Trafficking, Targeting and Interaction at the Glutamate Synapse" in *Neuroscience* 158(1) January 2009.



Neuroscience – the official journal of the International Brain Research Organization (IBRO)
– has been edited from CMBN 2006 – 2009

Neuroscience is one of the major international journals within the field of neurobiology and publishes results of original research on any aspect of the nervous system. The former CMBN Director Ole Petter Ottersen has served as Chief Editor of *Neuroscience* 2006 – 2009.

Other high-lights and events

Among the CMBN international representation activities was the Norwegian State visit by Their Majesties King Harald V and Queen Sonja to South Africa on November 24-27 2009, entitled “Economic growth through knowledge transfer” where also tuberculosis and aging were addressed.

Her Majesty Queen Sonja displayed enthused engagement at the State visit to South Africa

Industrial spin-offs

Bioinformatics

The company Sencel Bioinformatics AS was founded in June 2001. The company headed by Torbjøn Rognes, provides software tools to aid in genetic sequence analysis. It is based on bioinformatics research at the hospital. The name of the company stems from its mission to make sense of genetic data at an accelerated speed (www.sencel.com)

SENCEL™

Databases

Laboratory notebook and information system from Science Linker AS

Knut Petter Lehre invented a database solution to handle the data authentication and tracking needs of research groups, and brought a prototype of this system with him when he was employed at CMBN. The system was tested in Danbolt’s research group, and proved itself to be so powerful that it was decided to develop it further as a commercial product, and a company, Science Linker AS, was set up. Science Linker AS is a partner in one of the FUGE projects. The system is not only an archiving and tracking system, but also has modules for image analysis, chemical safety information, bibliographical data, e-mail, invoice handling, and breeding of transgenic animals. The latter module is now used at the Norweginan Institute of Public Health as their standard system for managing the animal facility.

New patent

Anti-microbial peptides – patent # 09172106.8 (M. Bjørås)

Additional diagnostic, therapeutic and preventive DOFIs and patent applications have been filed

Concluding remarks

In CMBN, 2009 has been clustered by scientific discoveries, research events and enhanced networking. 2009 was the year in which it became unequivocally evident how and why CMBN makes a difference in science in Norway, based on the progress and findings since the previous year. It is our goal to nurture the influence of molecular biology in neuroscience and vice versa. These fields are mutually refreshing each other, high-lighting that we together can create more. The 2009 achievements provide improved understanding of healthy aging and neurodegeneration, which in turn will lead to improved handling of brain disease.

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