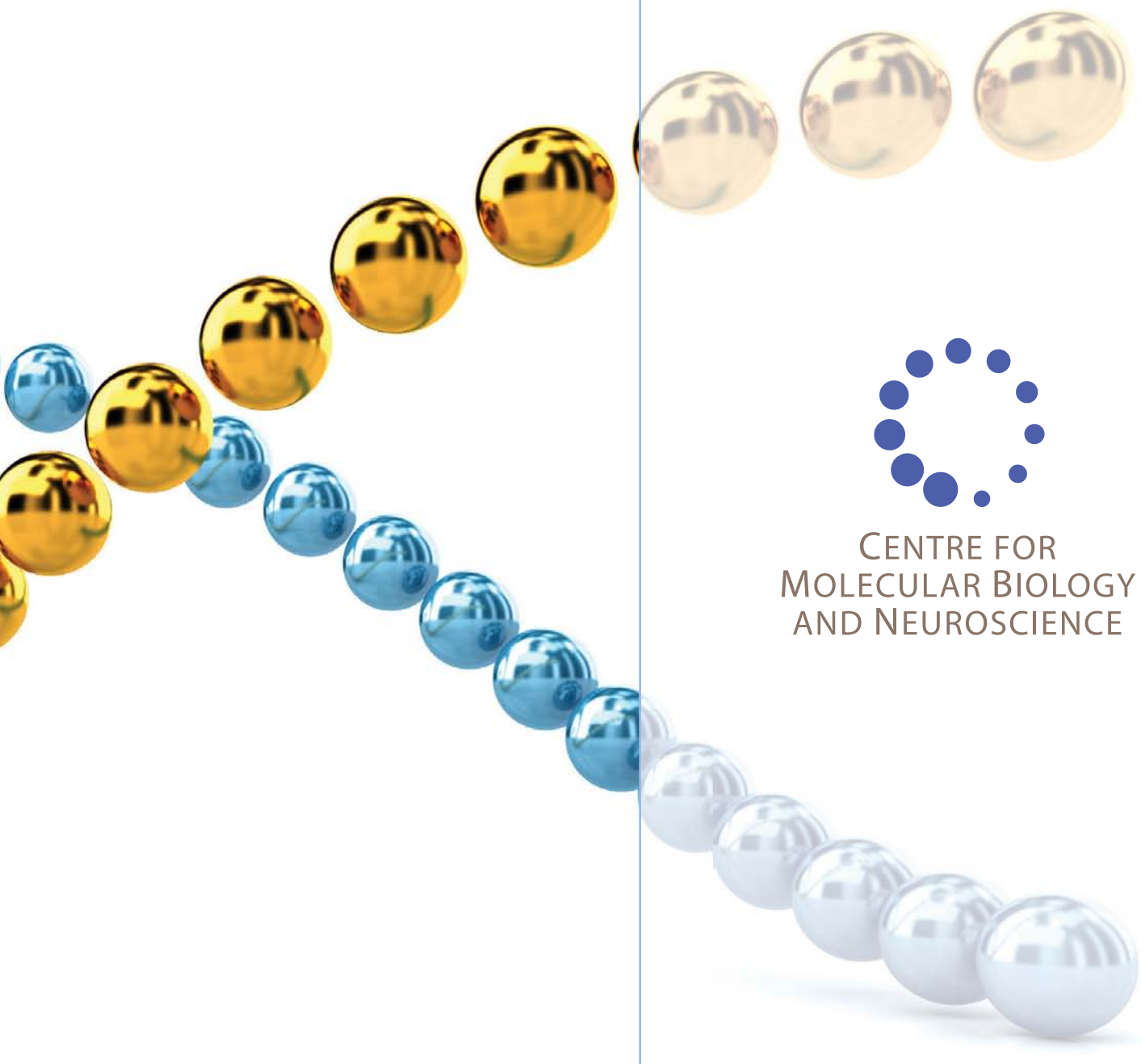
Centre for Molecular Biology and Neuroscience (CMBN)

annual report
2010



CENTRE FOR
MOLECULAR BIOLOGY
AND NEUROSCIENCE

Vision

"The vision of the Centre is to identify, develop and promote treatment for brain diseases and age-related neurological ailments"

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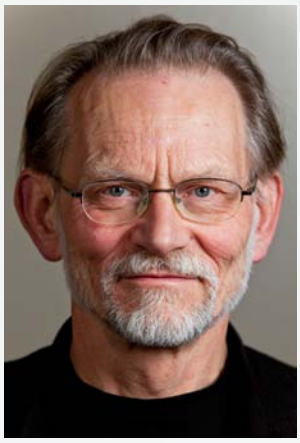
The directors' view of 2010

Tone Tønjum



Jon Storm-Mathisen

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

2010: Time for scientific change

We are in an era of *rapid scientific change* and rejuvenating development. Consequently, the scientific arena and experimental set-ups are clearly different from how things were in 2002, when the Centre for Molecular Biology and Neuroscience (CMBN) was established. For CMBN, the year has been filled by ample new scientific discoveries and events, locally and internationally. These activities all fuel the basic aim of the Centre, to be recognized as one of the most innovative research environments in identifying, developing and promoting new tools in the diagnostics and treatment of brain diseases and age-related neurological challenges. To achieve this goal, the Centre builds a thorough understanding of basic biological processes in health and disease. While the interactions between the core founding groups of the Centre underscore our vision, we are also seeing an increased number of collaborative projects that engage a number of other environments, including other centres of excellence, in Norway and abroad.

The main key to success is *quality in science*. Among the novel breakthroughs in 2010, CMBN scientists have deconstructed several complex machineries driving the brain and its maintenance at the DNA level, revealing new links to oxidative stress and mitochondrial defects inducing apoptosis and neurodegeneration. How these processes manifest themselves at the atomic, cellular and macro-anatomical levels has been elucidated in efforts that are more integrated between the scientific disciplines than before.

What does this mean for the future? It is clear that talent more than technology is what society or industry needs from enterprises such as CMBN. Research and the people trained in it inspire ideas, aspirations and actions that contribute to the vitality of society and its capacity for bold creativity in responding to whatever the future might bring. The prime function of front-line research is to develop new understanding and nurture the creative people who will carry it into society and bring society on.

The *creativity, energy and motivation of our young talents* continue to impress. A powerful and internationally competitive research base, essential to the present and future vitality of CMBN, depends fundamentally on a strong cohort of highly creative researchers, and therefore on our capacity to attract the best minds in each discipline from the global pool of talents.

Science education is a priority in CMBN, ranging from bachelor and master students to the fostering of new independent scientists. We have invested dedicated efforts to ensure that our most promising young scientists can position themselves for independent funding. In addition to an abundance of new large funding schemes pursued, this is one significant way of keeping competence on board.

CMBN is in itself an *incentive to bridge inter-disciplinary divides*. It has catalysed the establishment of new regional and national networks that already are generating translational research and innovation. The year 2010 has seen the rise of a new CMBN-derived national innovation cluster – or rather a knowledge transfer network – in neuroscience, the Nansen Neuroscience Network (NNN), which includes basic and clinical research environments, as well as relevant industrial partners. This initiative was launched by CMBN together with MI-lab in Trondheim as the other main driver on behalf of all neuroscientists in Norway and will promote innovation for the "Healthy Brain", helping to minimize the "translational block" by ensuring that discoveries in basic neuroscience are converted into improved prevention, diagnosis and therapy. NNN is also meant to increase the awareness of unmet needs in clinical practice. Innovation Norway has been most supportive in our endeavours to build improved alliances with industry and regional and national research institutions for forming NNN. We also

Message from Siri Hatlen, Chief Executive Officer, Oslo University Hospital

Siri Hatlen

feel that there is a general political backing for the NNN initiative. New innovations are emanating from CMBN and NNN – in the spirit of the recently merged Inven2 and well supported by this successful enterprise. Another initiative, where CMBN is a founding member, the Norwegian Brain Council (NBC, Hjernerådet), submitted its application to host the annual national NRK TV charity action. Despite the lack of initial success in this particular endeavour, other activities of the NBC have been most rewarding and the positive feedback generates trust that this application will be granted once the NBC is more established and recognized in society. Collectively, all of these activities contribute to building awareness of what brain disease is about.

The building of the new annexe to Domus Medica commenced on June 14, 2010, and efforts to meet the challenge of covering the expenses for scientific and inventory equipment were intensified in 2010. In collaboration with the CBM-Kavli Centre and MI-Lab in Trondheim, the revised NORBRAIN application for large-scale infrastructure to the Research Council of Norway (RCN) was re-submitted for the second round, after it was selected to be included on RCN's "Roadmap for infrastructure". Our intention is that the building and inherent technologies will serve the strong translational research network we are currently building. The fully functional Letten Centre was celebrated in March and September 2010; 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 EMBL node the Centre for Molecular Medicine Norway (NCMM). The NCMM, established 2007 with CMBN as a co-founder, was officially launched on November 11, 2010.

It is our dedicated and enthusiastic passion to maintain the chain of distinguished CMBN leadership, to ensure and boost its success. We are also most grateful to our host institutions, the University of Oslo and Oslo University Hospital, for generously accomodating us in a vivid way. The recent new discoveries in the pipeline for publication and expanding economy foretell further thriving of CMBN in 2011.

The vision for Oslo University Hospital is "Frontier research for better health; Oslo University Hospital shall deliver world-class research as well as lead and strengthen research in Norway, both nationally and regionally. Clinical activity, research and education should be tightly integrated and mutually beneficial in terms of improving quality and competence."

Centre for Molecular Biology and Neuroscience (CMBN) was the first Centre of Excellence at our institution and has been a major success with very favourable evaluations and high scientific output. Its multidisciplinary nature and integrated translational research contributes to Oslo University Hospital's activities by bridging the gap between basic sciences and clinical medicine. Excellence in science is the basis for rejuvenated and updated patient care.

Oslo University Hospital is a very good arena for translational research. Approximately 50 per cent of the medical research in Norwegian medical centres is performed at Oslo University Hospital, in close collaboration with the University of Oslo and an extensive national and international networking. High quality research that supports our prioritised areas of commitment also secures the operation and development of national and multiregional assignments. In this context, the efforts in research related to brain disease are within the prime strategic areas selected by the hospital. It is my belief that CMBN will continue to excel and contribute to molecular medicine beyond 2011.

Message from Frode Vartdal, Dean of the Faculty of Medicine, University of Oslo

Frode Vartdal

The Faculty of Medicine are proud to host the Centre for Molecular Biology and Neuroscience (CMBN). Since its establishment in 2002, CMBN has raised a number of outstanding young scientists. CMBN includes several research groups which are located in the premises of the University of Oslo (UiO), which is one out of two host institutions that contributes significantly to the funding of CMBN. One important issue that emerged in 2010 regards the need to secure the scientific career of our best talents in a time when permanent positions are in demand. The energy and motivation of our young talents continue to impress. Their resolve and stamina promises well for the future of CMBN. The young scientists constitute the most important asset of CMBN, and we will help to support their career development while positioning themselves for independent funding. As the new Dean of the Faculty of Medicine at the UiO, I feel that it is important to exert inspiring, good and clear leadership, so as to enable and support environments that will foster excellence in science and education. For this to happen, we will follow the new strategic plan of the UiO and the Faculty of Medicine. It is a privilege to enjoy good communication with both students, scientists and professionals, to work with such enthusiastic and competent colleagues, among which CMBN workers are most stimulating members. We will work to support and engender multidisciplinary research clusters, bridging the professional environments and institutes in joined efforts. The CMBN research groups have become increasingly important for the enhancement of both basic science and translational research at the UiO and Oslo University Hospital. Thus, many of CMBN research groups are increasingly involved in research on disease mechanisms in close collaboration with clinical scientists. Moreover, CMBN helps to provide many of the research groups at the UiO with state-of the art methodology thus contributing to efficient implementation of translational research activities. It is my belief that CMBN will continue to prosper and build bridges beyond neuroscience and molecular biology, between the UiO and the Oslo University Hospital, all in a strong international scenario.

Message from Jostein Chr Dalland, Chief Executive Officer, Inven2

Jostein Chr Dalland

Inven2, derived from Latin to invent, was established in 2010 as the merger of the two technology transfer offices (TTOs) Birkeland Innovation, University of Oslo (UiO), and Medinnova, Oslo University Hospital (OUH).

The merger makes ***Inven2*** the largest tech transfer and innovation company in Norway focusing on turning top science into business. As such ***Inven2*** represents the next generation innovation company servicing all research groups at University of Oslo, Oslo University Hospital and the south-eastern health region of Norway. Even though 2010 was highly influenced by the merger itself, Inven2 still delivered record high results with regards to number of inventions (186 DOFIs in total), patents (60 filings in 2010), and commercializations (22 in total). As such the potential going forward is exiting.

CMBN is a key actor in turning world class science into business

The life sciences sector represents a significant potential for value creation, and Centre for Molecular Biology and Neuroscience (CMBN) provides world-class science in an area of medicine and health in great demand, particularly for the future. Great science and scientist is a requirement to be able to create technology viable business. Many of the CMBN scientist are actively involved in translational medicine and innovation, and as a result 2 of 5 new spin-outs (new companies) established by Inven2 in 2010 are stemming from inventions made by CMBN scientists.

Strengthening the tie between scientific excellence in publication and first to invent

With CMBNs multidisciplinary nature and integrated translational research, CMBN not only contributes to excellence in science, but also as significant platform for innovation and ultimately commercialization. At the core of scientific innovation is the ability to identify and develop an invention as an opportunity. An increased awareness on the development of inventions will ultimately results in higher level of innovation. In this context, Inven2 offers early assessment of the commercial potential of the inventions (DOFI feedback) as well as support regarding patenting activities. Inven2 has both internal and external experts in the field of IPR and legal assisting the scientist to the benefit of CMBN generated ideas. This as part of Inven2s core activity in developing inventions into either spin-out companies or industry collaboration/licenses.

We believe in further growth in inventions stemming from CMBN

We believe CMBN will continue to accelerate and develop their innovation potential in the years to come. As such, we consider the impressive innovative results in CMBN in 2010 to be only a small fraction of what will be invented at the Centre in the years ahead. We are looking forward to further collaboration on exiting and new possibilities, and will do our outmost to further strengthening our good partnership.

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: 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

Professor Tone Tønjum is the Director of the Centre with overall scientific and administrative responsibilities for the activities of the Centre. In her duties, she is supported by Professor Jon Storm-Mathisen as Deputy Director and Ms. Kristine Aa.S. Knudsen as Administrative Head and Ms. Willemijn Solheim as the Administrative Consultant. The eleven group leaders create the Steering group of the Centre and they meet regularly to discuss important scientific, strategic and administrative issues.

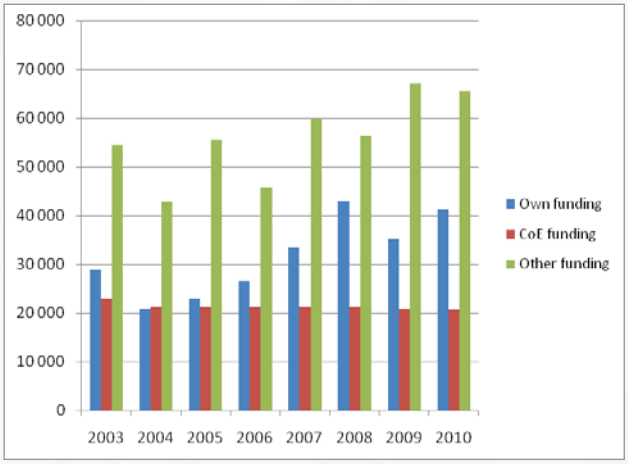
As the Centre of Excellence status is temporary, the Centre draws on the competence of the existing administrative staff at its host institutions, the Faculty of Medicine at the University of Oslo and the Oslo University Hospital (Rikshospitalet). Five of the eleven groups are located at Domus Medica, 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

Willemijn Solheim
CMBN Administrative Consultant

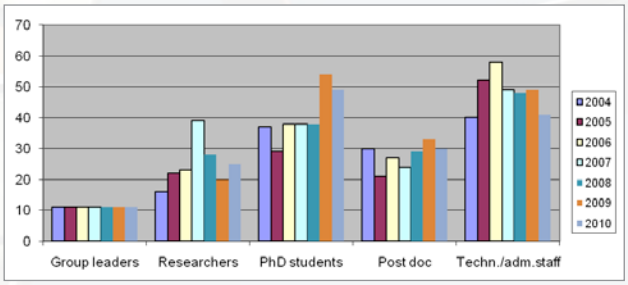
Economy

The Centre's total income was NOK 127.5 million in 2010, an increase of NOK 4 million from the year before. NOK 20 700 000 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 to 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 65 million. CMBN has throughout its time dedicated 1/2 of the funding from the Research Council of Norway for common infrastructure, heavy equipment with expert personnel and core facilities.



Personnel

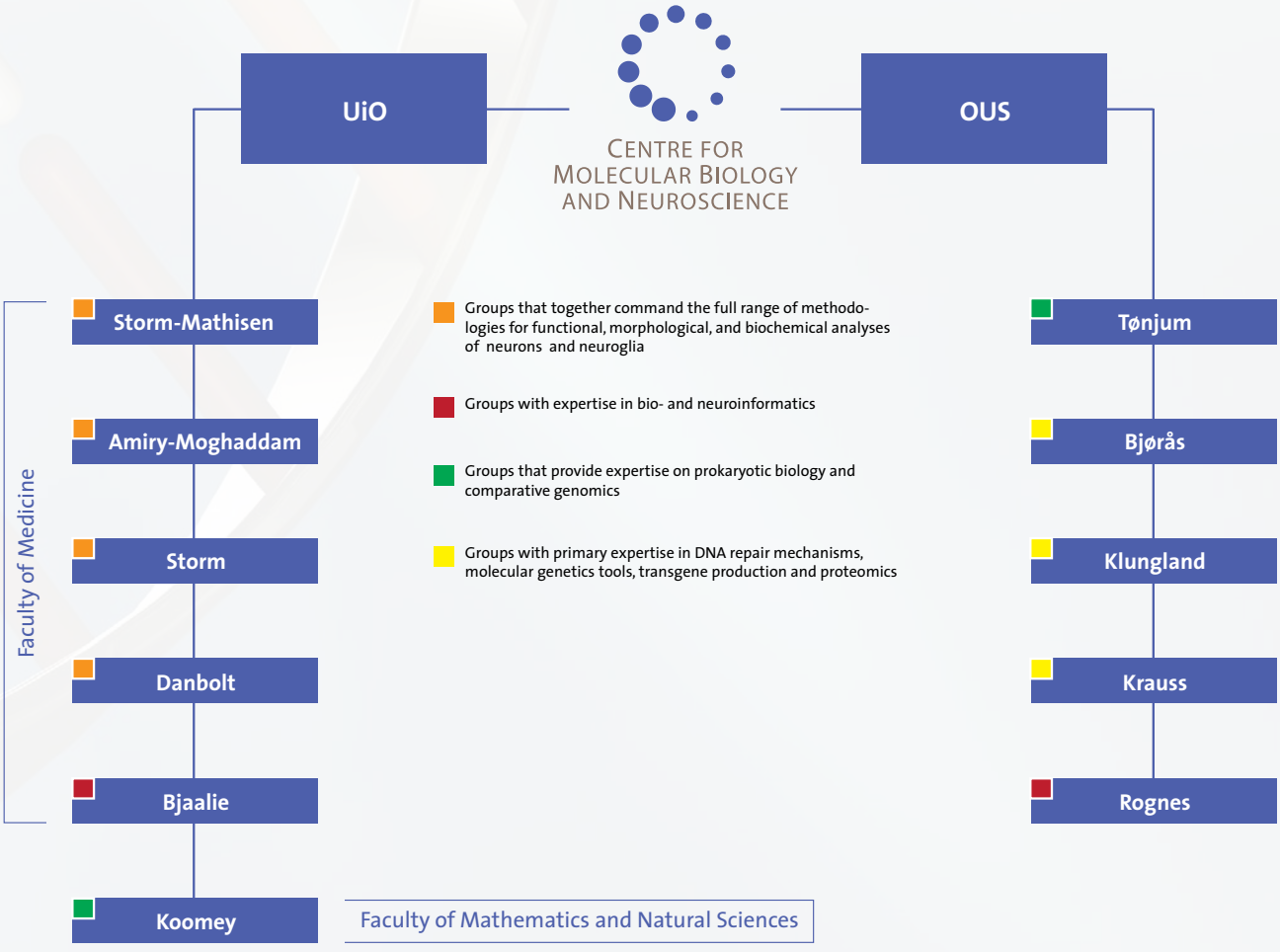
As one of the Centre's strategies is to be internationally leading within our scientific portfolio, it is of primary importance that the composition of our staff reflects this ideology. Only by conscious international networking and recruitment of staff can we secure this aim. The Centre had 25 foreign citizens from 15 different nationalities among its personnel. Out of the 12 guest researchers we hosted among the staff last year, only two 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, 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! --



The Genome Dynamics and Pathogenesis Group

Professor
Tone Tønjum

About

Microbial genomes are highly dynamic due to mutation, recombination and horizontal gene transfer. The stability of all genomes in general are also importantly challenged by DNA damage caused by endogenous and exogenous stress. Mechanisms for frequent genome variation, adaptation and maintenance are a necessity to ensure cellular fitness and survival in changing environments. Understanding pathogenesis, horizontal gene transfer, genome instability and DNA repair mechanisms requires an interdisciplinary approach of molecular biology, genomics and microbial physiology. Addressing these topics in major pathogens and model bacteria is most important for understanding the balance between fitness for survival and disease development. In particular, we are focusing on the identification of DNA binding components contributing to the neisserial transformation system which we suggest is directly coupled to pilus retraction. We have identified a number of novel DNA binding components and defined how they act and interact. We are also elucidating the effect of defects in DNA repair on host defence, and cellular fitness, and virulence in a new meningitis mouse model. The role of single nucleotide polymorphisms (SNPs) in DNA repair genes in brain aging and cognitive performance are addressed in a healthy human cohort as well as in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). The group addressing these challenges in molecular medicine through translational research is integrated into strong international networks.

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.

Challenges

To dissect how genome dynamics affect DNA sequence variability and conservation and thereby influence cellular fitness for survival and pathogenesis. To understand the evolution of transformation and sexual reproduction. To develop new strategies for diagnostics, prevention and treatment of disease.

Projects

- Deconstructing the meningococcal transformation machinery and search for novel vaccine candidates
- Mechanism and evolution of DNA sequence repeats and their influences on genome stability
- Effects of meningococcal brain infection on water homeostasis, brain edema and inflammation
- Role of DNA repair helicases in the genome maintenance of *Mycobacterium tuberculosis*
- The impact of DNA repair gene SNP profiles in normal human aging, AD and inflammatory bowel disease

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), discovering that transformation/sex is process with a conservative outcome that maintains genome stability (Genome Biology 2008), identifying DNA repair profiles in common bacterial pathogens (FEMS Microbiology Rev 2009), genetic predisposition for disease (Neuroscience 2007, CID 2008, FEMS Microbiology Rev 2009).

Paucity of mycobacteria in mucosal bowel biopsies from patients with early inflammatory disease (J. Crohns Colitis, 2010). Deconstruction of the neisserial DNA Uptake Sequence (International Pathogenic Neisseria Conference IPNC 2010). The genome-wide effects of transformation, mutation and phase variation in *Neisseria meningitidis* (IPNC 2010), role of DprA in neisserial transformation (IPNC 2010), cellular response to menigococcal meningitis (IPNC 2010), and the immunoprotective potential of the PilQ complex (IPNC 2010). Characterisation of the RecG enzyme from *Mycobacterium tuberculosis.*

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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 (such as ADHD, epilepsy, Parkinson, Alzheimer), and during ontogenetic development and ageing.

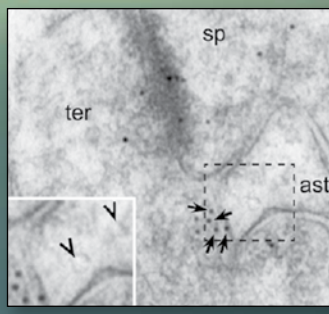
Challenges

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 can modulate neuronal function. Our main aim is to study synaptic function under physiological conditions and to investigate how the factors contributing to normal signalling are altered in disease, identifying new therapeutic strategies.

Projects

- 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 monocarboxylates (lactate, ketone bodies) in normal brain function, and in disease such as epilepsy; effects of physical activity.
- Synaptic changes during ontogenetic development and in animals with deficient DNA repair.

Recent achievements: Glutamamine transporters, SN (Cell 1999, EMBO J 2001, Eur J Neurosci 2002, Glia 2003, J Am Soc Nephrol 2005) and SA/SAT (PNAS 2000, J Neurosci 2002, J Cell Biol 2002) were molecularly identified and characterized. A role of glutamine has been defined for normal synaptic function (J Neurochem 2008) as well as dendritic retrograde signaling (Cereb Cortex 2009c), and a potential target uncovered in Alzheimer's disease (Neurochem Res 2008). The ultrastructural localization of monocarboxyltate transporters (MCTs) (Exp Brain Res 2001, Cereb Cortex 2005, Neuroscience 2007a) as well as identification of glutamate transporters in glia (Glia 2008) and in nerve endings (Neuroscience 2008) provides new approaches to understanding brain function. The identification of proteins, VGLUT1-3 (Neuron 2001, PNAS 2002), that pump glutamate into synaptic vesicles allows the packaging of the transmitter to be characterised in health and disease (J Comp Neurol 2004, 2006, 2007) and modified by gene knock-out (Science 2004). Astrocytes, triggered by e.g. purinergic receptors (Eur J Neurosci 2007), release glutamate from VGLUT containing vesicles to enhance synaptic efficacy (Nature Neurosci 2004, 2007, Neuroscience 2009a). The observations that astrocytes and even non-neural cells (J Cell Sci 2004, J Lipid Res 2007) store and can release neurotransmitter amino acids in a way resembling synaptic release, and that oligodendrocytes have NMDA type glutamate receptors (Nature 2005), together with findings that glutamate and other neuroactive substances can be co-released from nerve endings (Eur J Neurosci 2003, Molec Neurosci 2004, Cereb Cortex 2009a), including at the neuromuscular junction (Neuroscience 2007b), suggest novel ways of intercellular communication and potential drug targets. Observations in synapsin knock-out mice that develop epilepsy (Neuroscience 2005, Cereb Cortex 2009b) and in a rat model of ADHD (Neuroscience 2009b) implicate anomalous glutamate signalling in these diseases. Ionotrophic glutamate receptors are implicated in nociception (Mol Neurobiol 2009), 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). Downregulation of MCT1 in microvessels indicates deficient monocarboxylate transport across the blood brain barrier in human temporal lobe epilepsy (Neurobiol Dis 2010). Oligodendrocytes depend on lactate for survival and formation of myelin (J Neurosci 2010).



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).

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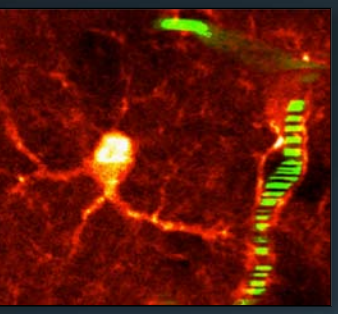
Laboratory of molecular neuroscience

Associate Professor Mahmood Reza Amiry-Moghaddam

About

The Laboratory for molecular neuroscience involve molecular mechanisms 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, epilepsy, Parkinson's disease and Alzheimer's disease and to develop novel approaches for the treatment of brain edema.



Two photon in vivo imaging of blood vessel (green) astrocytes (red) and calcium signalling in astrocytes cell body and processes (yellow).

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, epilepsy, 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) and other 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 and Alzheimer's disease

Recent achievments: Unraveling role of AQP4 in cell volume regulation and calcium signaling in astrocytes (Benfenati et al, PNAS In Press; Thrane et al PNAS. Epub 2010 Dec 27). Unraveling roles of water transporting co-transporter NKCC1 in formation of arachnoid cysts in human (Exp Neurol. 2010 Aug;224(2):424-8, Cerebrospinal Fluid Res. 2010 Jun 10;7:8.) and edema formation in mice (Neurocrit Care. 2010 Aug;13(1):123-31). Demonstration of Kir4.1 SNPs in human temporal lobe epilepsy (Epilepsy Res. 2010 Jan;88(1):55-64). Designing and synthesis of synthetic peptides potentially binding to AQP4 (Jacobsen et al. Org Biomol Chem. 2009 Apr 21;7(8):1599-611, and J Org Chem In Press)

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Laboratory for molecular biology

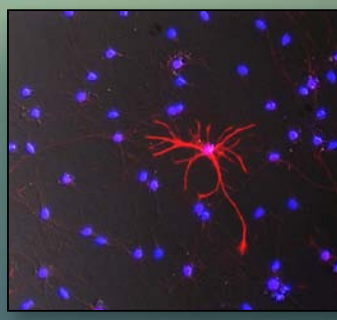
Professor
Magnar Bjørås

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, cell cycle regulation and adaptation. 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. Challenges are to understand the mechanisms for cellular protection against DNA damage and its role in cancer, ageing, stem cell maintenance and neurological disease.



En astrocytt blant differensierende nevronale stamceller.

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 cell cycle regulation 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: We identified four novel mutations in the DBT gene, encoding the transacylase subunit (E2) of branched chain alpha-ketoacid dehydrogenase complex, resulting in intermittent maple syrup urine disease in seven Norwegian patients. (Mol Genet Metab. 2010 Aug;100(4):324-32.)

We found that both all-trans retinoic acid and arsenic trioxide induce autophagy via the mammalian target of rapamycin pathway in APL cells and that autophagic degradation contributes significantly both to the basal turnover as well as the therapy-induced proteolysis of PML/RARA. Given the central role of the PML/RARA oncoprotein in APL pathogenesis, this study highlights an important role of autophagy in the development and treatment of this disease (Blood. 2010 Sep 30;116(13):2324-31.). We demonstrated reduced expression of DNA glycosylases in post-hypoxic newborn pigs undergoing therapeutic hypothermia. (Brain Res. 2010 Dec 2;1363:198-205) We demonstrated that mitochondrial DNA integrity is essential for mitochondrial maturation during differentiation of neural stem cells (Stem Cells. 2010 Dec;28(12):2195-204). We have identified a new 5' exon (exon 1) in the apn1 gene and show that the inactivity of S. pombe Apn1 is due to a nonsense mutation in the fifth codon of this new exon. Since all S. pombe laboratory strains originate from L972 h(-), it appears that all experiments involving S. pombe have been conducted in an apn1(-) mutant strain with a corresponding DNA repair deficiency. (DNA Repair (Amst). 2010 Dec 28.)

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Neural Systems and Graphics Computing Laboratory

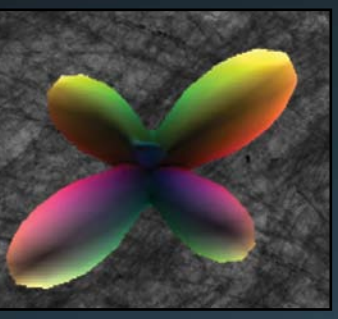
Professor
Jan G. Bjålie

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 atlasing

Challenges

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



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.

Projects

- *Neuroscience databases and atlasing systems.* We develop database applications for image data, from microscopy level to tomographic imaging data (PET and MRI). 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, advanced tomographic imaging techniques are employed to characterize structural and functional relationships occurring in the brain following experimental perturbations or disease.

- *Morphological phenotyping of small animal disease models.* Combinations of diffusion MRI and quantitative histological methods are employed to characterize neural network changes occuring in transgenic models for neurodegenerative 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, 2010, 5:e8595). 2) functional mapping of opioid receptor systems in the brain using positron emission tomography (Schoultz et al., 2010, Eur J Nucl Med Mol Imaging 37:1174-1180; Hjørnevik et al., Clin Phys Func Imaging 2010, 20:285-293), 3) 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). 4) 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.

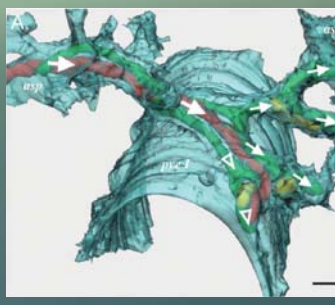
Challenges

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).

Projects

- Conditional deletion of genes (GAT2, GAT3, BGT1, EAAT2 and GS).
- The role of the GAT3 transporters in seizure control.
- The importance of EAAT2 in nerve terminals
- Determination of GABA and glutamate transporter distributions and densities around select synapses.
- Computer modelling of transmitter release, diffusion, removal and receptor activation in 3D-models of neuropil
- The roles of transporters in peripheral organs (endocrine pancreas, heart, kidney and liver).
- 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: To uncover the role of astrocytes in controlling water and ion exchange at the brain–blood interface, we have studied the endfeet coverage of the vessel wall by means of electron microscopic 3D reconstruction. The endfeet interdigitate and overlap, leaving no slits between them except for a few places where processes, possibly microglia, extend through the perivascular glial sheath to establish direct contact with the endothelial basal lamina. In contrast , the endfoot covering of the pericyte is incomplete, allowing neuropil elements to touch the basal lamina that enwraps this type of cell. Thus, free diffusion is limited to narrow clefts between overlapping endfeet. Further, we have studied the role of the betaine-GABA transporter (BGT1) in seizure control. Recently, the investigational drug EF1502 was found to exert an anti-convulsant action supposedly due to inhibition of BGT1. We have deleted exon 3-5 of the BGT1 (slc6a12) gene thereby abolishing the expression of BGT1 mRNA and protein. This, however, does neither affect normal development nor the seizure susceptibility in a variety of seizure threshold models including: corneal kindling, the minimal clonic and minimal tonic extension seizure threshold tests, the 6 Hz seizure threshold test, and the i.v. pentylenetetrazol threshold test. BGT1 mRNA is present in the brain, but at levels that are several hundred times lower than those of the major GABA transporter GAT1. Thus, it seems unlikely that BGT1 plays any role in the brain at all.



Endfoot processes (blue) containing elongated mitochondria (green and red). The footplate is complete and covers about half the circumference of the vessel wall. Elongated mitochondria (arrows) enter the endfoot tangentially through the left process and leave through four processes on the right hand side. Scale bar 1 um (Mathiisen et al., 2010).

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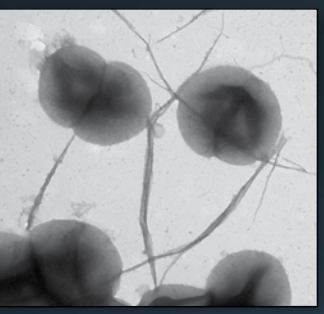
Molecular and cellular basis of microbial pathogenesis

Professor Michael Koomey

About

Our laboratory uses human associated species of the 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 (PTMs) of surface proteins. We have focused primarily on these processes in the closely related species *N. gonorrhoeae* (causing gonorrhea) and *N. meningitidis* (causing epidemic meningitis). In particular, we want to understand what factors dictate the propensity for *N. meningitidis* to colonize the nasopharynx and cause meningitis whereas *N. gonorrhoeae* resides at genital sites. This work is supplemented by studies of commensal *Neisseria* that harmlessly colonizes the nasopharynx.



Neisseria gonorrhoeae/ expressing type IV /pili// /(electron microscopy image).

Challenges

Protein glycosylation has significant effects on protein properties and is well established in a variety of pathogens and symbionts of man. We have discovered at least thirteen glycoforms in *Neisseria*. However, the benefits afforded by bacterial protein-associated glycans and their variability is still poorly understood. Challenges are to understand the role of these PTMs and their extensive variability in pathogenic *Neisseria* and related species. We use research strategies combining biochemistry, bioinformatics, and reverse genetics together with advanced mass spectrometric-based proteomic approaches to examine PTM status.

Furthermore, the evolutionary relationships between *Neisseria* are poorly characterized and little is known about the factors that determine the unique human interactions exhibited by pathogens and commensals. Recently, we found rare genetic changes in core metabolic glycoproteins that were phylogenetically informative and affected core respiratory processes. This encouraged us to study their role in evolution and niche adaptation.

Projects

- The diversity of protein-associated glycans in *Neisseria* and its genetic basis.
- We have developed an assay related to pilus biogenesis, showing that phosphoform- and glycan-modifications affect bacterial survival. Understanding the basis for this lethal effect could shed light on general functional benefits of protein glycosylation in bacteria.
- Dynamic and functional interplay between glycosylation and zwitterionic phospho-from modifications
- Roles and evolutionary importance of glycoproteins in terminal respiratory pathways (oxygen targeting and denitrification)

Recent achievements: We have devised a systematic approach to correlate gene repertoire with protein-associated glycoform structure in *Neisseria* (Børud *et al*, 2010). We discovered rare genetic changes in a core respiratory protein that are phylogenetically informative and affect core respiratory processes (Aspholm *et al.*, 2010). We showed that multiple pilus motors cooperate for persistent bacterial movement (Holz et al., 2010), that infection of mucosa by *Pseudomonas aeruginosa* requires mutually dependent virulence factors and a novel pilus-associated adhesin (Heiniger *et al.*, 2010), performed functional analyses of pilin-like proteins from *Francisella tularensis* and complementation of type IV pilus phenotypes in *Neisseria gonorrhoeae*.(Salomonsson *et al.*, 2010).

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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 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.

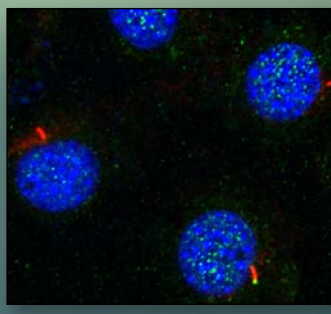
Challenges

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

Recent achievements: b -catenin is a central factor in a variety of solid tumours. Using chemical screens we have identified a series of antagonists to canonical Wnt signalling that prevent b -catenin from entering the nucleus. Using *in vivo* models we have shown that the antagonists ǀW74 and ǀW55 efficiently prevent tumour initiation.



FLAG-tagged Gli2 localization in primary cilia upon activation of Hh signalling by the SMO agonist SAG (green: FLAG-tagged Gli2; red: acetylated tubulin; blue: DAPI). Martin Strand / Eline Buchman.

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Bioinformatics group

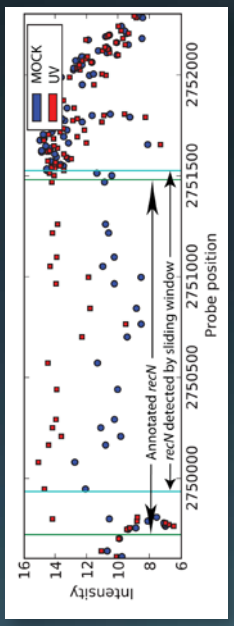
Associate Professor
Torbjørn Rognes

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.

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.



The transcriptional activity along the entire E.coli genome in UV treated and untreated (mock) cells was measured using custom designed tiling microarrays. The image illustrates the transcription surrounding the known SOS response gene recN. The sliding window algorithm developed detects the coding part of recN with an almost perfect overlap to the annotation, and the upregulation of recN in the UV treated bacteria is easily seen. Intensity is given on a log2 scale.

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? How have the genes evolved? Docking and molecular dynamics simulations are also used in our studies.

- **Tools for sequence analysis:** 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. We are working to improve such tools further. New methods for mapping of short sequence reads from deep sequencing are also being developed.

Recent achievements: Characterized transcriptional profile of *E.coli* under UV radiation and identified differentially expressed small peptides (PLoS One, 2010). Identified patterns of continuous and periodic of expansion of CAG repeats in Huntington's disease mice (PLoS Genet, 2010). Discovered the mutation in the *S.pombe* AP endonuclease (DNA repair, 2011).

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Laboratory for genome repair and regulation

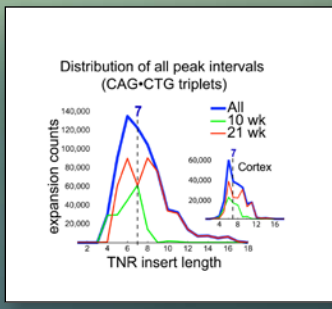
Professor
Arne Klungland

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. The major rationale behind studying DNA repair and DNA Regulation (including epigenetics), is the remarkable similarity, both at the sequence and biochemical levels, between enzymes introducing and removing macromolecular modifications, regardless of whether the target is DNA damage or an epigenetic mark. We focus mainly 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.



A histogram of insertion lengths for all CAG expansion events from Huntington transgenic mice measured in 69 separate striatum samples (blue). Both mean and median values of the distribution point to a dominant insertion length of seven CAG repeats. The separate contributions from 10-week (green) and 21-week (red) data are also shown. Inset figure shows a similar result for cortex, with the insertion length distributed at 7 repeats, despite the smaller number of insertion events observed in total. (From Møllersen, Rowe et al., PloS Genetics 2010).

Projects

- **DNA Repair**: Role of FEN1 in DNA repair and replication with focus on cancer development.
- **Huntingtons Disease:** Modelling triplet expansion in Huntington disease mice and role of DNA repair.
- **Epigenetics:** Understand, in detail, the maintainence of modifications on DNA and histones involved in reprogramming. Recognize the accurate role of Alkbh1-8.

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) we show that others have roles in epigenetic reprogramming (PloS One 2010), 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, Nature Comm. 2011). 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). We have also established a novel method for the efficient identification of 5-hydroxymethylCytosine (5hmC) in genomic DNA (NAR 2011). Finally, extensive analysis of CAG triplets of ageing Huntington mice, combined with advanced bioinformatical analysis by the Rognes group, has identified two modes of somatic CAG expansion (PloS Genetics 2010).

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Laboratory of cellular neurophysiology and ion channel function

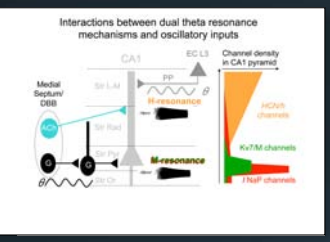
Professor
Johan F. Storm

About

Our group is interested in mechanisms of brain function, from molecules to behaviour. We study fundamental principles and mechanisms of neural signalling and coding 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) in brain slices and *in vivo*, molecular genetic (viral vectors and transgenic mice) and pharmacological manipulations, computational modelling (Neuron, SurfHippo), and behavioural testing.

Challenges

To determine the functional roles and interplay of multiple signalling mechanisms within dendrites, axons and other neuronal compartments, 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.



Cartoon illustrating proposed functional roles of the dual theta resonance mechanisms recently discovered by Hu et al. In hippocampal pyramidal cells.

From: Hu H., Vervaeke K., Graham L.J., Storm J.F. (2009). Complementary theta resonance filtering by two spatiallysegregated mechanisms in CA1 hippocampal pyramidal neurons. Journal of Neuroscience. 29: 14472-83.

Projects

- Functional roles and mechanisms of neuronal oscillations and resonance in the mammalian cortex.
- The roles of voltage-gated ion channels in neural coding, signalling, synaptic plasticity, learning and memory.
- Changes in neuronal signalling during development and ageing.
- 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.
- Roles of Ca2+-activated K+ channels (BK and SK channels) in neuronal signalling, synaptic plasticity, cognitive functions, motor control, epilepsy and neuroprotection.

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; Liao et al. PLOS 2010). 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).channels are essential for cerebellar learning and motor control (Proc Natl Acad Sci USA 101: 0474-8, 2004).

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CENTRE FOR
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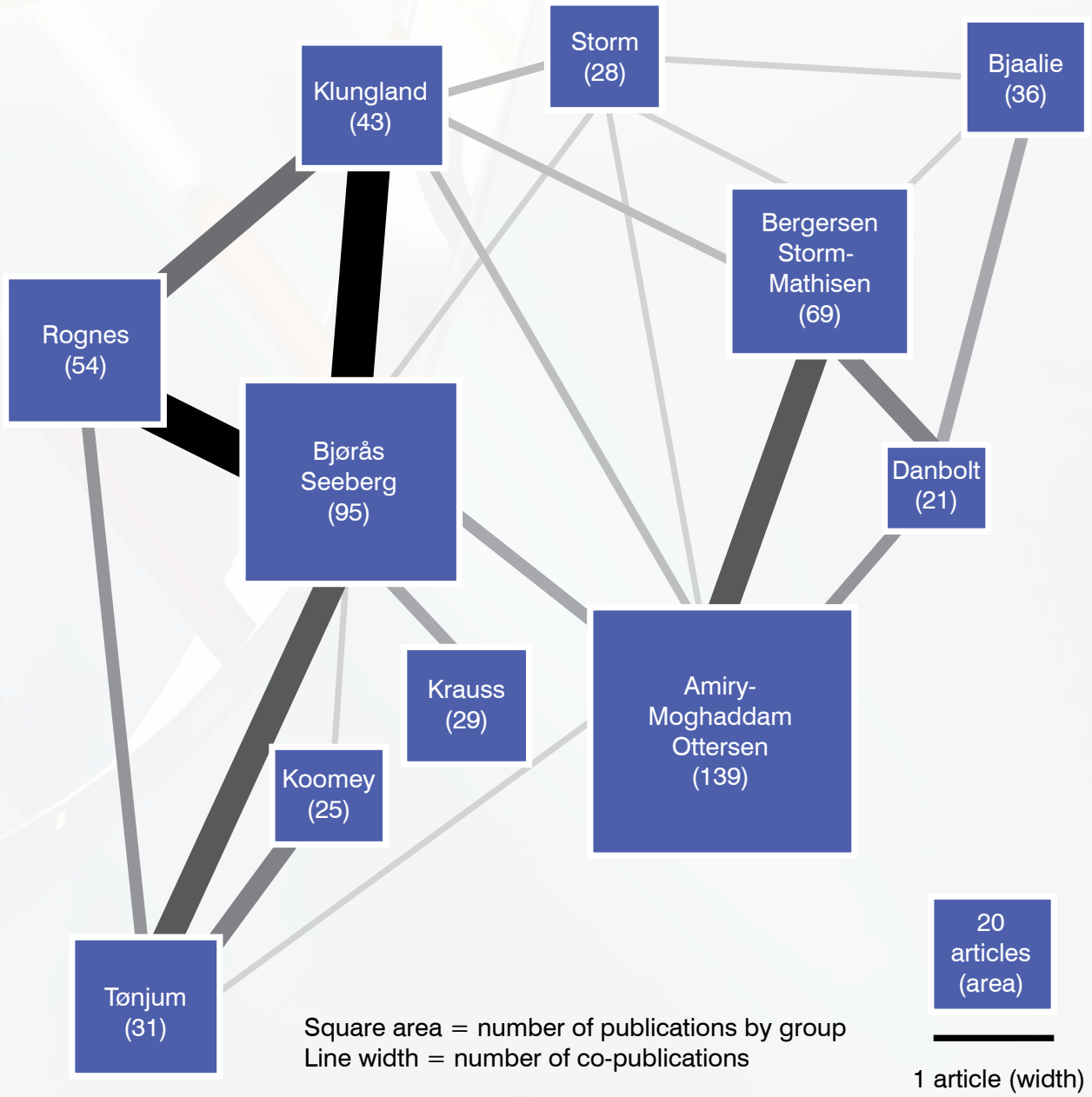
CMBN group co-publications



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Neurology, 75 (17), 1527-32
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(Impact 8.2)

2. **Amiry-Moghaddam M**, **Hoddevik EH**, **Ottersen OP** (2010)
Aquaporins: multifarious roles in brain
Neuroscience, 168 (4), 859-61
PubMed 20450960

3. **Aspholm M**, **Aas FE**, Harrison OB, Quinn D, **Vik A**, **Viburiene R**, **Tønjum T**, Moir J, Maiden MC, **Koomey M** (2010)
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PubMed 20808844
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PubMed 20537169

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PubMed 20570198

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An overview of Cdk1-controlled targets and processes
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Unstable DNA repair genes shaped by their own sequence modifying phenotypes
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Proc Natl Acad Sci U S A, 107 (9), 4206-11
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A Distinct Slow-Cycling Cancer Stem-like Subpopulation of Pancreatic Adenocarcinoma Cells is maintained in vivo. *Cancers* 2010, *2 (4), 2011-2025*

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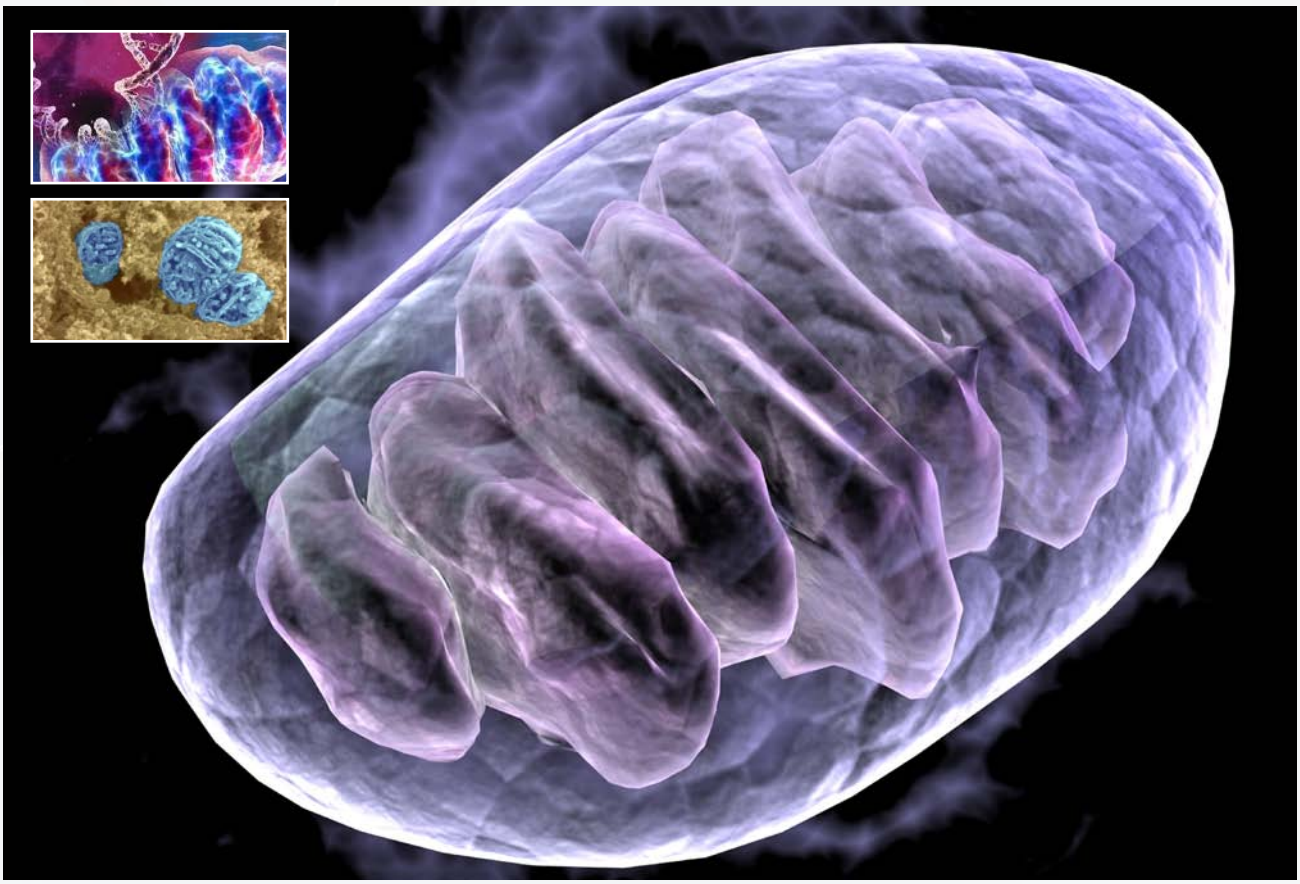
Publications high-lights 2010

In each of our cells, on average 50-70 000 damage events take place in the DNA every day. These damages also happen in cells that do not replicate and have a life-long time span, such as most brain cells. CMBN scientists have shown that DNA repair in the brain is very abundant. If the repair processes do not occur as normal, the DNA can be changed and the consequences can be premature aging, cancer or neurodegenerative brain disease such as Altzheimer's or Huntington's disease (Møllersen et al., PloS Genetics 6 (12), e1001242, 2010). Consequences of a defect the DNA repair component AlkB can in addition to neuron damage induce congenital eye malformations (Nordstrand et al., PloS One 5(11) e13827, 2010). Research on these processes is the core activity of CMBN.

Scientists at CMBN together with German collaborators have in 2010 described mechanisms for rapid synaptic activation between interneurons in the hippocampus, the brain structure associated with learning and memory (Hu et al., Science 327 (5961), 52-8 , 2010; Hu et al., Proc Natl Acad Sci USA 107 (2), 894-9, 2010). Another discovery is on how important stem cells and mitochondria are for efficient repair in the brain (Wang et al., Stem Cells 28, 2195-204, 2010). Other major discoveries address the role of mitochondria in aging and neurodegeneration (Mol Cell Biol 30, 1357-67, 2010). Mitochondrial DNA damage induce apoptosis and degradation of neuroner, characteristic of neurodegenerative diseases, particularly in the hippocampus, highly relevant for the pathogenesis of Alzheimer's disease (Songe-Møller et al., Mol Cell Biol 30, 1814-27, 2010).

CMBN scientists have also discovered that the system for normal autophagy, cellular self-digestion, is particularly active in blood cancer cells (Bø and Simonsen, Autophagy 6, 964-5, 2010; Blood 116, 2324-31, 2010). Autophagy is particularlY relevant for macrophage function in brain diseases such as Alzheimer's.

In general, major leaps have been undertaken in the understanding of brain disease (Mathiisen et al., Glia, 58 (9), 1094-103, 2010) and bacterial evolution (Aspholm et al., PLoS Pathogens 6 (8), e1001055, 2010), which collectively provide extended insight into how cells function and develop and, in turn, will represent new potential for early diagnostics, prevention and treatment.



Mentor activities

CMBN graduate student Meryl S. Lillenes is currently the head of the PhD forum board at AHUS. Their main function is to represent the PhD students and promote their opportunities for learning and networking, as well as organize interesting seminars on relevant topics for PhD students. They also organized an advanced seminar in presentation techniques with great success. Further, this activity will expand to establish a PhD forum at OUS/RH in order to give PhD students there the benefit of the useful and social environment of a common professional-educational forum.

CMBN graduate student Meryl S. Lillenes

PhD degrees 2010

1. **Sigve Nakken**
   Inference of molecular mechanisms from sequence patterns in human DNA variation
   Faculty of Medicine, University of Oslo, 8 December 2010
   Supervisors: Torbjørn Rognes and Eivind Hovig

2. **Ragnhild Weel-Sneve**
   Microbial RNomics and the role of small transmembrane peptides in genotoxic stress control
   Faculty of Medicine, University of Oslo, 7 December 2010
   Supervisor: Magnar Bjørås

3. **Trine Hjørnevik**
   Studying nociceptive processing in the rat brain by PET imaging and digital atlasing
   Faculty of Medicine, University of Oslo, 22 October 2010
   Supervisor: Frode Willoch

4. **Nina Therese Solberg**
   Aspects of canonical Wnt signaling in the developing mouse forebrain
   Faculty of Medicine, University of Oslo, 1 September 2010
   Supervisor: Stefan Krauss

5. **Johanne Egge Rinholm**
   Energy Supply and Signalling in Grey and White Matter Structures of the Brain
   Faculty of Medicine, University of Oslo, 31 August 2010
   Supervisor: Linda H. Bergersen

6. **Gard O. S. Thomassen**
   Design, analysis and applications of custom high-density oligonucleotide microarrays
   Faculty of Medicine, University of Oslo, 10 June 2010
   Supervisor: Torbjørn Rognes

Achievements in 2010

John Arne Dahl, Adam Robertson and Arne Klungland received the 2010 Inven2's innovation prize, 3rd place for their method for sensitive detection of methyl groups. The prize was announced in Oslo City Hall on October 21, 2010, at a joint event organized by Oslo Municipality, Innovation Norway and NHO.

Anders Jahre prize for best publication in 2009

Structures of endonuclease V with DNA reveal initiation of deaminated adenine repair.

Bjørn Dalhus, Ida Rosnes and Magnar Bjørås at CMBN were in 2010 awarded the Anders Jahre prize for the best publication in 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

Core facilities at CMBN

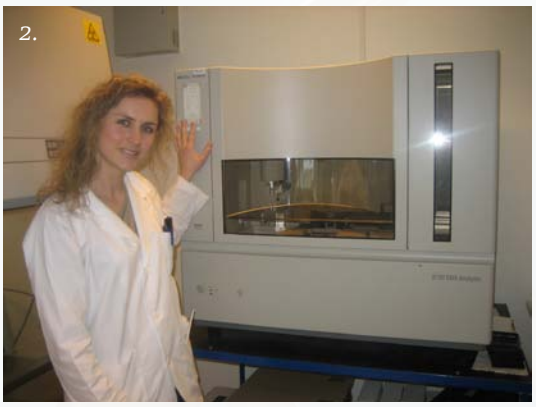
CMBN invests 35% of its RCN funding in infrastructure and core facilities, to the benefit of all CMBN workers and the research environment in general

- DNA sequencing
- Mass spectrometry: Orbitrap
- Structural biology/ X-ray crystallography
- Thyphon Imaging
- Confocal microscopy
- Electron microscopy
- Two/Multi Photon microscopy
- High throughput tissue processing
- Neuro/bioinformatics
- Transgene technology

Example images:

1. LTQ Orbitrap: high-resolution mass spectrometry
2. ABI 3120: High through-put DNA sequencing, run by Mari Støen/Tone Tønjum
3. Technai electron microscopy, run by Bashir A. Hakim
4. Zeiss confocal microscopy, run by Laura Camassa/ Lasse Ormel


1.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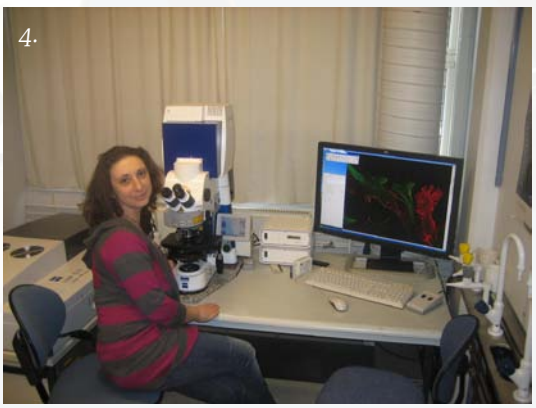
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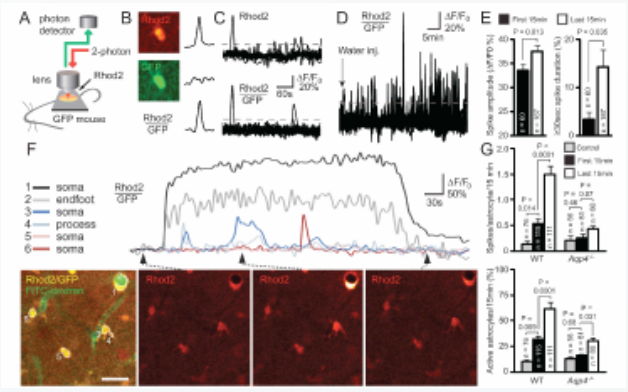
Letten Centre

Letten Centre, CMBN's facility for *in vivo* two-photon laser scanning microscopy, was completed in 2010. A generous donation from the Letten Foundation in 2008 made it possible to establish the centre. The brain imaging facility is headed by NCMM group leader Erlend A. Nagelhus who currently heads a team of 10 staff members dedicated to studying synapse dynamics and roles of aquaporins at the glio-vascular interface.

Postdoc John M. Burkhardt (Photo: J.G. Lothe)

Postdoc Karolina Szokol (Photo: J.G. Lothe)

In collaboration with Maiken Nedergaard's laboratory in Rochester, NY, the Nagelhus' team published a paper in Proceedings of the National Academy of Sciences of the U.S.A (Thrane et al., Proc Natl Acad Sci, Epub 2010 Dec 27). The paper showed for the first time that aquaporins modulate glial Ca^{2+} signaling and ATP release. The article attracted a "Research Highlight" comment in Nature Reviews Neuroscience (Welberg L. Glia: Aquaporin: not so swell? Nat Rev Neurosci 12, 66, 2011).



Modulation of glial Ca^{2+} signaling by aquaporins, as shown by in vivo two-photon imaging (Thrane AS, Rappold PM, Fujita T, Torres A, Bekar LK, Takano T, Peng W, Wang F, Thrane VR, Enger R, Haj-Yasein NN, Skare Ø, Holen T, Klungland A, Ottersen OP, Nedergaard M, Nagelhus EA. Critical role of aquaporin-4 (AQP4) in astrocytic Ca2+ signaling events elicited by cerebral edema. Proc Natl Acad Sci, Epub 2010, Dec 27).

CMBN and gender equality

The CMBN recruits many promising young scientists for the future. We are very proud that more than 50 % of the PhD students and postdoctoral candidates at CMBN are women. In spite of the high recruitment of young women doing outstanding science, only two out of eleven group leaders at CMBN are women.

CMBN has the aim to encourage and enable equality between the genders. In 2010, CMBN received a grant from the UiO to support the gender equality work. Our focus is to encourage women to take on leading positions in the science community. To support them in doing so, we are organizing seminars and generating networks for highly competent women at CMBN and the professional environment.

Seminar I: "How to grow as a scientist". Three inspiring role models told their story on how to succeed in science, Sigrun Halvorsen (OUS/Ullevål), Olaug Villanger (OUS/Rikshospitalet) and Anne Simonsen (UiO/Med Fac). Notably, Kajsa Widen, Lund University, talked about their project and educational program that aim to make women become leaders in academia.

Seminar II: Mentoring: The aim of the seminar was to enable female scientists who have a carrier in academia to meet and exchange experience and ideas on the role of mentorship. Linda Vidal from AFF, Bergen, presented introductory views on the topic and led the discussion.

Seminar III: External 2-day retreat at Lysebu addressing "Strategies for career development for women". Both young and experienced researchers participated in a workshop led by Foresight Norway on how to work with the challenge of taking responsibility for your own future carrier. Inspiring talks by Inga Bostad, Assistant Rector, UiO, Ulla Wever, Dean of the Faculty of Life Sciences, University of Copenhagen, Denmark, Siri Gedde Dahl, journalist in Aftenposten, and Preben Z. Møller, writer and sociologist. In addition, Ingrid Uldahl presented the new strategic plan for gender equality at the UiO.

Kristine Bonnevie - 1911

Marie Sklodowska Curie - 1921

Helga Eng - 1926

The Kavli Prize

CMBN Co-Director Jon Storm-Mathisen serves as Chairman of the Kavli Prize Committee on Neuroscience, which for the 2010 prize consisted of the following other members, appointed by the Norwegian Academy of Science and Letters (DNVA) among outstanding neuroscientists 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 9, 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 2010 neuroscience winners are:

RICHARD H. SCHELLER
Executive Vice President, Genentech, US

THOMAS C. SÜDHOF
Professor, Department of Molecular and Cellular Physiology Stanford University School of Medicine, US

JAMES E. ROTHMAN
Professor and Chairman, Department of Cell Biology at Yale University, US

The Kavli Prize Symposium in Neuroscience was on September 6, 2010
Organized by LH Bergersen, E Moser, MB Moser, J Storm-Mathisen

Richard Scheller, Genentech, Pomas Südhof, Stanford University, og James Rothman, Yale University, mottar Kavliprisen i nevrovitenskap av H.M. Kong Harald. (Foto:Terje Bendiksby/Scanpix)

Conferences, symposia and seminars

CMBN has a thriving activity with frequent seminars in addition to the weekly meeting series, with no less than 23 international guest lecturers invited in 2010. A selection of conferences in 2010 are listed below

Geust Lecture Baroness Susan Greenfield

Thursday January 21, 2010, Baroness Susan Greenfield CBE, Director of the Royal Institution of Great Britain and Professor of Pharmacology at the University of Oxford, gave a guest lecture on: The **Future of the brain - the brain of the future**

Greenfield has expressed concerns that modern technology, and in particular social networking sites, may have a negative impact on child development. She leads a multi-disciplinary team investigating neurodegenerative disorders.

Progress in Neuroscience Symposium, June 11-12

CMBN scientists together with the Medical Faculty of the University of Oslo, Unit for Research in Clinical Neuroscience, Oslo University Hospital, and The Norwegian Academy of Science and Letters organized the symposium: **Progress in Neuroscience.** A tribute to Per Andersen's lifelong commitment.

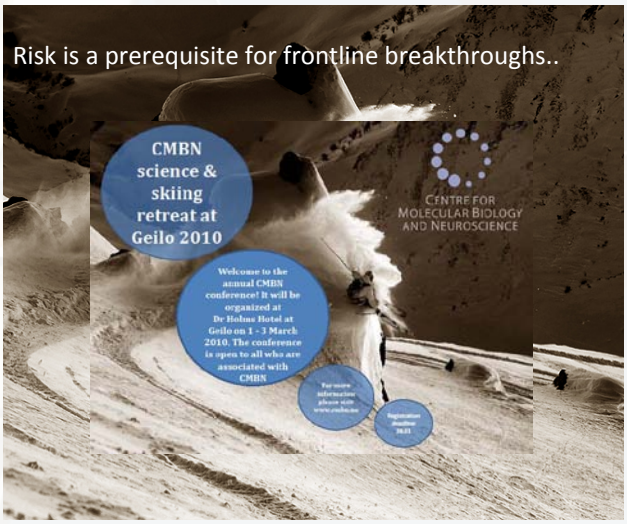
Thanks – for nearly 60 years in neuroscience.

National Dementia Symposium

On october 8-9, 2010, Nansen Neuroscience Network and H. Lundbeck A/S together with CMBN organized a national dementia symposium attended by more than 220 scientists and clinicians at the Grand Hotel in Oslo.

http://www.oslo.teknopol.no/Hovedmeny/Aktuelt/Kalender/Nasjonalt-Demens-Symposium/

The CMBN Science and skiing retreat was organized at Geilo on March 1-3, 2010

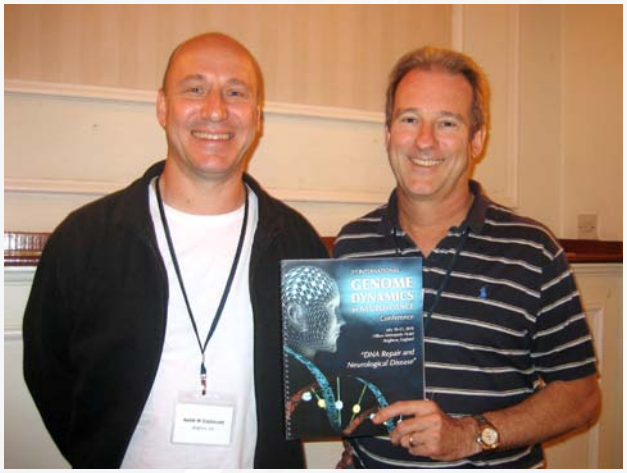


The third Genome Dynamics in Neuroscience Conference 2010 (GDN3)

In 2006, CMBN initiated the "Genome Dynamics in Neuroscience" meeting series in Oslo, while the second meeting was held in Asilomar, California US, in 2008.

On July 18-21 2010, the third "Genome Dynamics in Neuroscience" meeting (GDN3) took place in Brighton UK, with Keith Caldecott UK and Peter McKinnon US as the main organizers (www.stjude.org/GDN2010).

CMBN has provided scientific, organizational and financial support to each of the GDN meetings. The scientific output from GDN3 was of high quality and most timely and will be further enhanced by a special issue with original articles and reviews in the Journal Mechanisms of Aging and Development dedicated to the meeting.



Caption: Keith Caldecott UK and Peter McKinnon US

Mini-symposium: "Mental Illness: Bipolar Disorder and Depression"

CMBN in collaboration with the Norwegian Honorary Consulate General in Minneapolis arranged a Mini symposium on: **Mental Illness: Bipolar Disorder and Depression**

Welcoming addresses by Tone Tønjum, Director of CMBN, and Ellen Sue Ewald, Director of Higher Education and Research, the Norwegian Honorary Consulate General in Minneapolis.

Kjell Magne Bondevik, President of the Oslo Centre for Peace and Human Rights, spoke about: Overcoming Stigma of Mental Illness, while Professor S. Hossein Fatemi, University of Minnesota Medical School, addressed: Clinical and Molecular Aspects of Bipolar Disorder: A Paradigm for Major Mental Disorders and Professor Jim Fallon, University of Irvine, California coevered: The Neuroanatomy of Depression.

The Norwegian Honorary Consulate, General Honorary Consulate General in Minneapolis

Nansen Neuroscience Lectures October 10, 2010

In commemoration of Nansen's birthday on October 10, 2010, CMBN, in collaboration with the Norwegian Academy of Science and Letters, organized the first Nansen Neuroscience Lectures, on Monday 11 October 2010 at Domus Medica, University of Oslo. Speakers: Albert Gjedde, Copenhagen; Kenneth Hugdahl, Bergen; May-Britt Moser, Trondheim. Organizers: Linda H. Bergersen and Jon Storm-Mathisen.

Career development seminar for women

CMBN invited to a seminar on scientific career development for women, attended by 45 female scientists, on October 21-22, 2010, at Lysebu

CMBN in the media

Tiårets forskningsgjennombrudd
Morgenbladet, 24 December 2010

Dette er en del av bløffen
Nettavisen Side2, 11 December 2010

Til bunns i hjernens vannkanaler (bilde 1)
Forskningsrådet, 18 June 2010

Jakten på intelligensgener
Kronikk av Farrukh A. Chaudhry og Joel Glover
Morgenbladet, 14 May 2010

Månedens forsker May 2010: - Nøkkelen til det gode liv ligger i genene
Helse Sør-Øst, 6 May 2010

Draumedag med blod på hendene
Uniforum, 19 April 2010

Cocktail mot aldring
Apollon, 22 March 2010

Debatten, 18 March 2010 - "Hjernevask"
Nett TV, NRK, 18 March 2010

Ny kunnskap om Parkinsons sykdom (bilde 2)
Tidsskrift for Den norske legeforening,
11 March 2010

Forsker på cocktail mot aldring (bilde 3)
VG (print edition, p. 22), 26 February 2010

Lovende stamceller (bilde 4)
kronikk av Elisabeth Larsen (PhD, CMBN & Rikshospitalet)
Aftenposten, 23 January 2010

Baronesse Susan Greenfields besøk i Oslo,
Oxford Lecture

Skjermfolket tar større risiko
Uniforum, 26 January 2010
http://www.uniforum.uio.no/nyheter/2010/01/skjermfolket-tar-storre-risiko.html

Hjernen blir annerledes i fremtiden
Aftenposten, 25 January 2010
http://www.aftenposten.no/fakta/innsikt/article3482160.ece

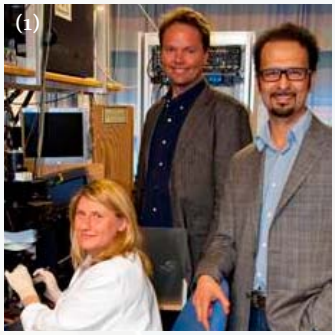
Lita forandring kan styra overlevingsevna til gonorébakterien
http://www.uniforum.uio.no/nyheter/2010/09/knekteoverlevingskoden-til-gonor%C3%A9bakterien.html

Stamcelleforskning kan løse kreftgåten
http://www.forskningsradet.no/no/Nyheter/Stamcelleforskning_kan_lose_kreftgaten/1253961224567?WT.mc_id=nyhetsbrev-ForskningsradetNorsk

Krefthemmende legemiddel skal utvikles
http://old.helse-sorost.no/modules/module_123/proxy.asp?C=124&I=1811&D=2

Kavliprisen i nevrovitenskap 2010
http://www.biokjemisk.com/files/resourcesmodule/@random4c86587ed107c/1289293295_NBS_nytt_06__2010.pdf (side 6)

Stress gir sårbare stamceller (bilde5)
http://www.forskningsradet.no/servlet/Satellite?c=Nyhet&cid=1253963080570&p=1224698072633&pagename=nevronor%2FHovedsidemal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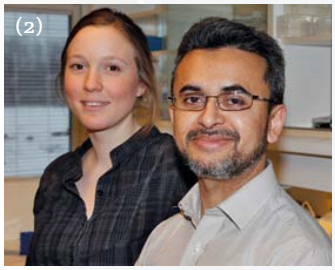
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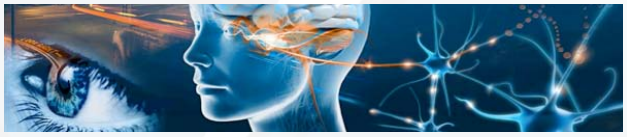
NANSEN NEUROSCIENCE NETWORK
connecting brain science and industry

Nansen Neuroscience Network

Following the initiative from CMBN, UiO and MI Lab, NTNU, on behalf of all Norwegian neuroscientists, and supported by Innovation Norway, the Nansen Neuroscience Network was founded on May 11, 2010.

The inaugural session, chaired by CMBN Co-Director Jon Storm-Mathisen, was opened by the Minster of Health Anne-Grete Strøm-Erichsen, and the meeting had a list of distinguished speaker including President and CEO of Innovation Norway Gunn Ovesen, Rector of the University of Oslo Ole Petter Ottersen, CEO Helse Midt-Norge Gunnar Bovim, and CEO of the LMI, Karita Bekkemellem.

By the end of 2010 the organization has nearly 40 members equally distributed among major research institutions, start-up companies and major international corporations (www.nansenneuro.net)



The NNN networking vision

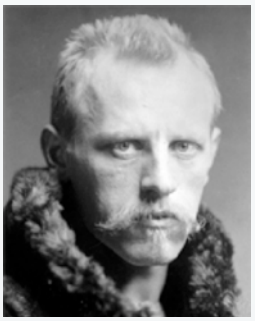
Being the driving force in connecting brain science and industry, aiming at creating smart solutions for individuals and society and committed to improve quality of life through innovation, research and development of diagnostics, therapeutics and preventive measures.

Some of the major medical challenges of the 21st century are related to the increasing age of the population, which will lead to a dramatic increase in the prevalence of some of the most devastating and costly neurological disorders, such as Alzheimer's disease, Parkinson's disease, other forms of dementia and stroke. Progress in neuroscience can potentially not only offer effective strategies for prevention, early diagnosis and treatment for these age-related diseases, but also provide a better understanding of serious neuropsychiatric and brain disorders. While this would lead to enormous savings on health care costs, the improved quality of life for those affected cannot be overestimated.

From bench to bedside

A bottleneck in many fields of medical research resides in the translation from basic research to industrial development and clinical practice. We envisage that the progression from discovery to applied medicine would be much facilitated by strengthening the links between basic research and health care providers, in collaboration with industry and commercial partners to achieve five major goals:

- Facilitate the flow of ideas and products in the direction of the end users (patients and society).
- Facilitate communication of unmet needs from end users to basic and clinical scientists.
- Improve quality of life for the individual and reduce cost for the society.
- Stimulate the development of a profitable industry with novel products and services.
- Ensure increased political awareness of the importance of basic research in health care



Nansen Neuroscience Network inauguration

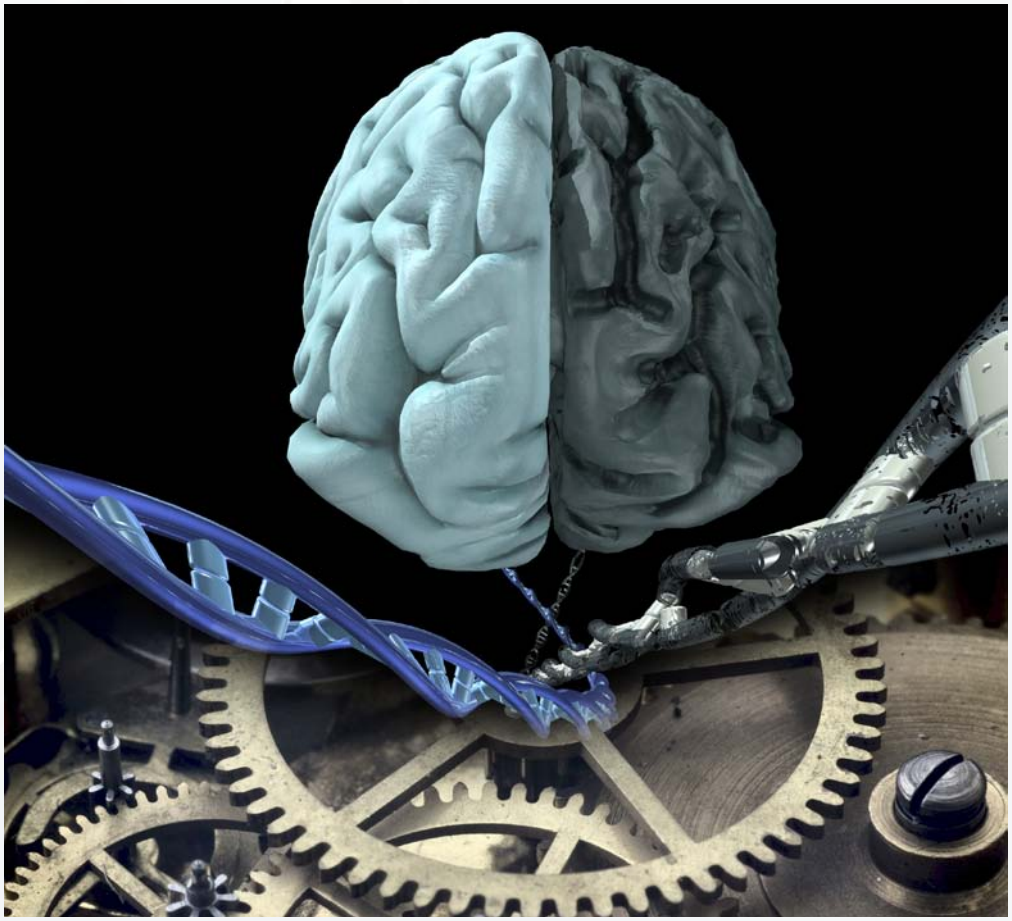
The establishment and inauguration meetings of the Nansen Neuroscience Network was held **Tuesday May 11 2010 at CMBN and at** the Radisson Blu Plaza Hotel, resepectively

Domus Medica II-annex

Building of the new Domus Medica II-annex commenced on June 14, 2011. CMBN has, together with the Faculty of Medicine and the Faculty of Odontology, been engaged in the establishment and invested much time into the planning of this advanced life science and teaching building throughout the years 2002-2010.

Concluding remarks

In 2010, CMBN activities have been fuelled by scientific discoveries, research events and formally established networking. 2010 was the year in which it became unequivocally evident how and why CMBN makes a difference in sciencific change, progress and development in Norway, emanating on the findings from previous years. It is our goal to continue 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 new synergies. The 2010 achievements provide improved understanding of the aging process, DNA repair in the brain, mitochondrial function and neurodegeneration, which in turn will lead to improved handling of the healthy and diseased brain.



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