CENTRE FOR
MOLECULAR BIOLOGY
AND NEUROSCIENCE

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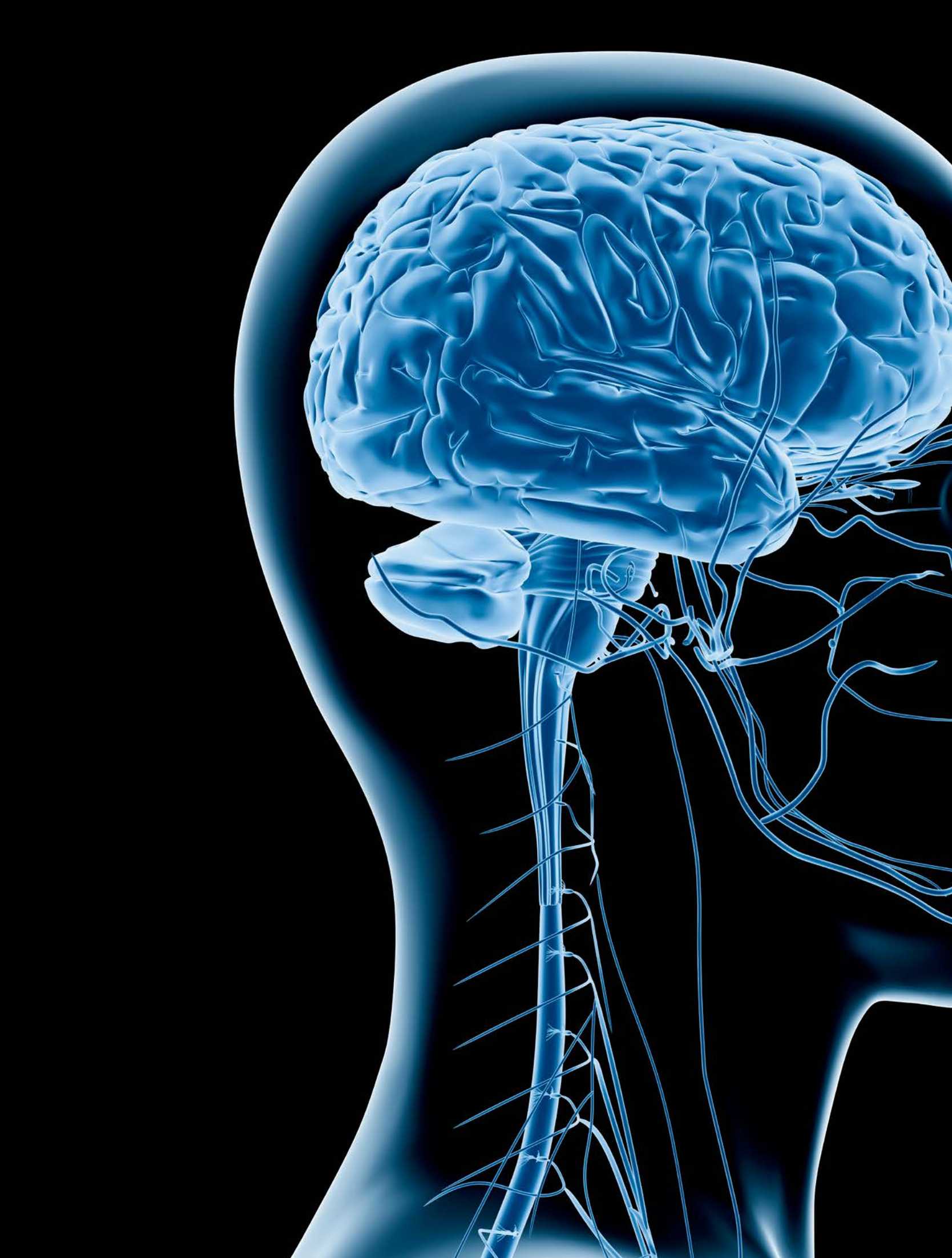
2012 ANNUAL REPORT & 10 YEAR SUMMARY



CENTRE VISION

The Centre shall take on a leading role in elucidating the impact of DNA repair and genome maintenance mechanisms in preventing neurological disease and brain aging.

(from the 2001 CMBN application to the RCN)

SUBGOALS

V1: "The Centre shall take on a leading role in elucidating the role of DNA repair and genome maintenance mechanisms in preventing neurological disease and brain aging."

V2: "The Centre shall provide fundamental new insight in the dynamics of molecular organization and functions of glutamatergic synapses and neurons, thus paving the way for rational therapeutic strategies targeted to the main excitatory fibre system in the brain."

V3: "The Centre will develop and apply stem cell technology and targeted repair to broaden the range of therapeutic strategies in neurological disease."

V4. "The Centre will further develop world-class expertise within microbial pathogenesis related to human disease in general and neurological disease in particular."

V5: "As spin-offs from its research activities, the Centre will deliver diagnostic and bioinformatics tools of considerable socio-economic and potential commercial value."

V6: "The Centre will take on a primary responsibility for postgraduate teaching in the research field at the crossroads between molecular biology, genetics and neuroscience."

(from the 2001 CMBN application to the RCN)

CMBN KEY FACTS

Norwegian name:
Senter for molekylærbiologi og nevrovitenskap

English name:
Centre for Molecular Biology and Neuroscience (CMBN)

Primary funding:
Centre of Excellence / Senter for Fremragende Forskning SFFI project of the Research Council of Norway
2002-2012

Staff/Faculty:
11 research groups, approximately 200 scientists, staff and students

Host institutions:
University of Oslo (UiO) and Oslo University Hospital (OUS)

Research objective:
To understand how nerve cells communicate with one another and define the role of DNA damage / maintenance and other factors in human brain disease and brain aging

Publications:
700 articles / publications in internationally-recognized, peer-reviewed journals

Research training:
65 doctoral degrees awarded

Outcome:
Successful integration into the host institutions is secured by the establishment of three Scientific Excellence Research Thematic Areas (SERTAs) representing the main scientific legacy of CMBN. The new SERTAs will be entitled SERTA Healthy Brain Aging (HBA), SERTA Genome Integrity (GI) and SERTA Developing and Adaptive Brain (DAB), hosted by the UiO and OUS

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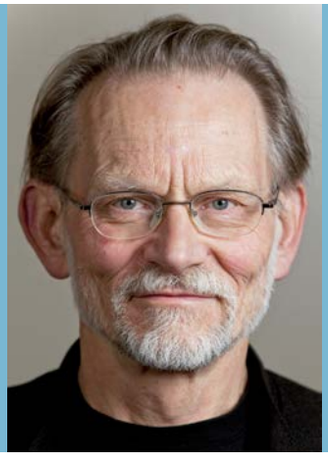


The Directors' view 2012

Tone Tønjum
CMBN Director

Jon Storm-Mathisen
CMBN Co-Director

DRIVING THE FRONTLINE OF INTERNATIONAL RESEARCH

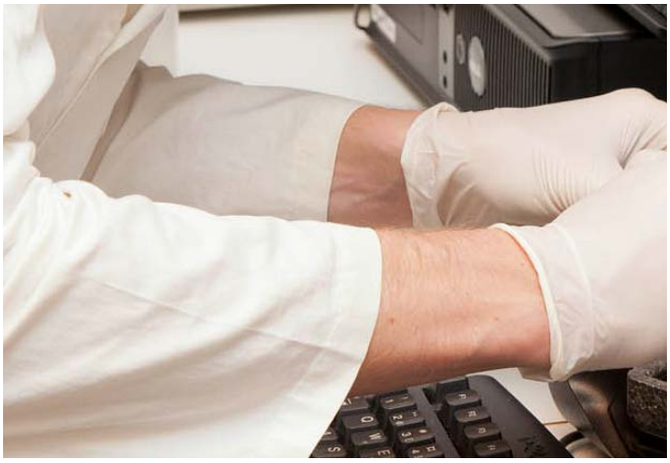
2012 has for CMBN been filled with scientific discoveries and innovation, spiced by interactive events, locally and at the international level. These activities all nurture the basic aim of the Centre, to be recognized as one of the frontline international research environments. CMBN scientists are identifying and developing new methodologies in the diagnostics, prevention and treatment of 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 have also seen an increased number of collaborative projects that engage other environments, including other centres 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 keep an open and clear attitude in the interpretation of the findings. Thirdly, but not the least, the signature of CMBN is to host unique competence, diversity and complementarity, with both young and senior scientists engaged in internationalization activities. The CMBN publication record for the years 2002-2012 is evidence of the success of our interdisciplinary endeavour, signifying our strive to make an excellent research environment outstanding.

An essential goal for CMBN is to promote quality in science. 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 are generating translational research and innovation.

Opened 2012, the new Domus Medica annexe with its high quality mark is a signature building for the life sciences in Norway. Our goal is to fuel all the technologies that will be allocated in the new building. These include high throughput tissue processing, mass spectrometry/structural biology, neuro/bioinformatics, live imaging and transgene technology. In this context, a number of new large funding schemes have been successful, including the RCN-funded NORBRAIN infrastructure, a partnership between the Kavli Institute and MI-Lab at NTNU and CMBN at the University of Oslo. The building, its unique scientific environment and technologies will host and serve strong translational research networks nationwide. The nationwide benefit of the NORBRAIN investment, and the legacy of CMBN, will be enhanced by CMBN's partnership in the nationwide Norwegian Research School in Neuroscience (NRSN), granted by RCN November 2012.

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 CMBN



is the investment in young talented 'Principal Investigators' to secure their scientific career ahead, so that they can establish new groups. We have 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.

International networking has flourished in 2012, highlighted by the fourth Genome Dynamics in Neuroscience meeting addressing genome instability and DNA repair in the context of neuroscience and aging in a multidisciplinary setting. The conference brought together world-leading scientists to discuss the state-of-the-art and current perspectives on the role of genome instability and bioenergetics in normal brain ageing and in the pathogenesis of neurodegenerative diseases. A special issue in the journal Mechanisms of Ageing and Development entitled "Genome Dynamics Shaping Neuroscience" is a by-product of the meeting. No project is more successful than its exit strategy. We are committed to securing the CMBN legacy, to maintain the competence on board and nurture the most valuable scientific qualities of CMBN. At this stage of the CMBN project, a bottom-up plan has been secured by re-shaping the three centre of excellence-application environments, addressing the healthy brain, brain adaptation and development and genome integrity, respectively, into new Scientific Excellence Research Thematic Areas (SERTAs) at the Faculty of Medicine at the University of Oslo. In general, we are particularly grateful to our host institutions, the University of Oslo and the Oslo University Hospital, for generously accommodating us, first as a CoE and subsequently as SERTAs to continue developing scientific output through the next decade. Finally, CMBN is most thankful to the RCN for the CoE funding!

It is our humble and enthusiastic dedication to maintain the distinguished line of science that has emanated from the CMBN, to secure the outcome of the Centre. Our ambition is to inspire the creativity, competence and productivity of our eminent CMBN scientists and students, to ensure and boost their success, and thereby the legacy of the CMBN.

Message from Ole Sejersted, Chairman of the CMBN Board

Congratulations, CMBN!

A ten-year period as a Centre of Excellence has been accomplished with great success and important scientific achievements. Although the Centre period is now coming to an end, it is time for celebration since what has been built in these years cradles promising aspects for the future. The intellectual and technical capital that has accumulated can now be invested into new projects that will resonate in the whole scientific community. There have been some concerns that this big investment might not have lasting effects, however, all of the 11 CMBN partner groups have skillfully made strategic moves to preserve and build on what has been achieved. The University of Oslo has provided a solid framework and support that will ensure that this effort will be successful. Oslo University Hospital has been and will continue to be an important partner and support. I wish to commemorate Professor Erling Seeberg who was Deputy Director of the Centre until his untimely death. His leadership and his scientific contributions were outstanding. I wish to commend Professor Ole Petter Ottersen, now Rector of the University, for his enthusiasm and vision that were so important for establishing the center and for his excellent leadership during more than 6 years. He was succeeded by Professor Tone Tønjum with Professor Jon Storm-Mathisen as Deputy Centre Director. They have skillfully prepared the Centre for the changes that will come through a successful exit strategy and new initiatives. For me, the task as chairman of the board during these ten years has been easy and rewarding thanks to the proficient Centre leaders and thanks to professional support from the two host institutions – University of Oslo and Oslo University Hospital. Finally, I wish to thank all members of CMBN for the important contributions they have made and I wish you all to excel in science.

Message from Erlend Smeland, Director of Research, Education and Innovation, Oslo University Hospital

The First Centre!

Centre for Molecular Biology and Neuroscience (CMBN) was the first Centre of Excellence in biomedicine in Norway and the first at our institution. When the 10 year period for the centre now soon comes to its end, it is a great pleasure to observe that the contributing groups have performed scientific work of very high quality, as judged by very favorable reviews during the period and from a number of articles published in internationally top-rated journals. In fact, articles form the centre have twice been selected among the 6 best articles published at Oslo University Hospital (OUH) during a half year period - of approximately 750 articles. These newly established article prizes have so far only been delivered two times.

Excellent research is an important basis for updated patient care of high-quality. CMBN has contributed significantly to strengthening of the translational research, which is an important goal for the hospital. Its multidisciplinary nature has contributed to bridging the gap between basic sciences and clinical medicine. Of note, the research related to molecular medicine and brain disease are within the prime strategic areas of the hospital. Furthermore, very important research infrastructure has been built up during the existence of the centre.

The CMBN milieus are robust and active and receive substantial external funding. With the high quality of the research personnel and the strong scientific output, it is our strong belief that the groups will continue to play important roles for the development of molecular medicine and for the research at OUH, even under altered organizational structures after the formal closure of the CoE.

Message from Peter Agre, CMBN Guest Professor

Twenty years ago, I had the incredible good fortune to be contacted by Ole Petter Ottersen, a young Norwegian neuroscientist with remarkable insight and great energy.

Our team at Johns Hopkins had just identified the aquaporin channels that facilitate water transport into and out of cells, but we were unprepared to take the next steps. Together we have undertaken a series of exciting collaborative studies that are still continuing. Moreover, this provided us the opportunity to directly participate in one of Scandinavia's most amazing scientific institutions – the University of Oslo's Centre for Molecular Biology and Neuroscience (CMBN). The faculty, trainees, and staff of CMBN have established themselves as world leaders in understanding how the brain functions in health and disease. The importance of CMBN is still emerging, but I think it is likely that when the history of neuroscience is finally written, the major chapter will have its setting in Oslo. Congratulations to everyone in CMBN on your many outstanding achievements.

Message from Vilhelm Bohr, CMBN Guest Professor

Congratulations to CMBN for a job well done!

Through my friendship and collaborations with Erling Seeberg, I became aware of the early planning for CMBN and some discussions regarding its scope. I was very pleased to become a guest professor later on as it developed and have followed its course with great interest. The idea of combining genome stability with neuroscience was most timely and with good insight and foresight. Not only has CMBN been extremely successful, but it has also been an instigator and a part of a new field developing. CMBN has been hugely successful by many measures. Frontline research has been generated, new areas of research have been spawned, a tremendous amount of research money has been brought in, and new collaborations and friendships have been generated. It has been impressive for me to see how investigators not only have collaborated, but have actually moved their research focus in a different direction based upon stimulation from within. The management has done a superb job in making all this possible. It has been a great pleasure and honor for me to be part of CMBN.

Message from Ole Kristian Hjelstuen, CEO of Inven2

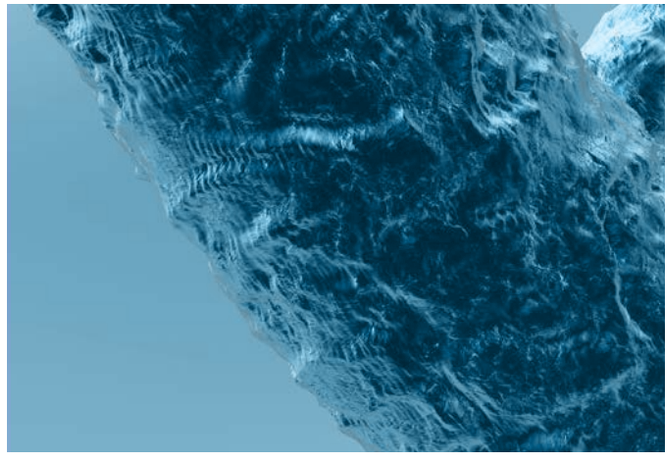
Centre for Molecular Biology and Neuroscience (CMBN) has been a key actor in turning world class science into business over the last 10 years.

The life sciences sector represents a significant potential for value creation, and CMBN provides world-class science in an area of medicine and health in great demand. Great science and scientists are key requirements to be able to create technology viable business. Many of the CMBN scientists are actively involved in translational medicine and innovation. With CMBNs multidisciplinary nature and integrated translational research, CMBN has not only contributed to excellence in science, but also as significant platform for innovation and ultimately commercialization.

Inven2 is Scandinavia's most efficient technology transfer organization, making 28 successful commercializations in 2011. The Inven2Biologics portal is now established to further promote the commercial potential. In the portal, scientists can register their reagents and research tools, spanning from mouse models and cell lines, to vectors and antibodies. There is a great interest in the life science industry to gain access to better evaluation tools, and Inven2Biologics offers an easily accessible overview of what is available. The portal is particularly well suited for the scientists at CMBN and will not only leverage on the commercialization potential of these brilliant scientists, but can also give the research groups additional opportunities to partner with industry.

We consider the impressive results in CMBN in 2012 and the 10 years before to be a significant contribution to society. Inven2 wants to use the opportunity to thank CMBN for our strong partnership.

Organization and economy



THE CMBN FOUNDING BOARD MEMBERS 2003-2006

The Board is responsible for ensuring that CMBN develops in accordance with the current research plan and according to its statutes. The Board consisted of:

Prof. Ole M. Sejersted, OUS/UIO, Chair

Prof. Olli Janne, University of Helsinki

Director Per Morten Vigtel, Investorforum

Senior scientists Inger Nina Farstad, Rikshospitalet

Chief physician Prof. Peter Gaustad, Rikshospitalet/UiO

Prof. Borghild Roald, Ullevål Hospital/UiO

THE CMBN BOARD 2007-2012

Prof. Ole M. Sejersted, OUS/UIO, Chair

Prof. Kirsten Sandvig, OUS/UiO

Prof. Torgeir Bruun Wyller, OUS/UIO

Prof. John Torgils Vaage, OUS/UIO

Mari Trommald, Helse SørØst (through spring 2011)

Prof. Lars Terenius, Karolinska University Hospital Sweden

The Centre is founded on a decentralized, organizational model that has proved to be conducive to the fulfillment of the research commitments embodied in the Centre's research plan, which was based on expertise and ideas of the 11 founding group leaders (GLs). The Centre leader is spokesman and ambassador for the Centre. A prerequisite in this capacity is legitimacy as an active researcher. The specific tasks in the research plans are conducted by the individual GLs, and coordination of the activities is secured through the GL-based Steering group. The Steering group made up by the CMBN group leaders (GL) has functioned as the over-riding strategic body for the scientific development of the Centre. The work of the Steering group has been based on a mutual Consortium agreement. The interdisciplinary cooperation and the obligations formulated in the research plan are anchored in the Steering group. The individual group leader benefits from freedom to govern the respective group, but with clear obligations with regard to following the Centre's joint research plan. CMBN's organization model with extensive delegation of tasks to the GLs has allowed the Centre leader to maintain a high profile research activity.

Ole Petter Ottersen, CMBN director (2002 - 2009)

Erling Seeberg, CMBN co-director (2002 - 2004)

CMBN FOUNDING DIRECTORS

Ole Petter Ottersen, Director (2002-2009)

Erling Seeberg, Co-Director (2002-2004, deceased)

CMBN CURRENT DIRECTORS

Tone Tønjum, Co-Director (2005-2009), Director (2009-2012)

Jon Storm-Mathisen, Co-Director (2009-2012)

CMBN GROUP LEADERS IN THE STEERING GROUP

Mahmood Amiry-Moghaddam
Magnar Bjørås
Jan G. Bjålie
Niels Chr. Danbolt
Arne Klungland
Mike Koomey
Stefan Krauss
Torbjørn Rognes
Johan F. Storm
Jon Storm-Mathisen
Tone Tønjum

In 2004 Magnar Bjørås replaced Seeberg; in 2009, Mahmood Amiry-Moghaddam replaced Ottersen, and Linda H. Bergersen became group leader of the Storm-Mathisen group.

ADMINISTRATION/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, Ms. Kristine Aa.S. Knudsen as Administrative head and Ms. Anne Haukvik 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 UiO and the OUS (Rikshospitalet). Five of the eleven groups are located at Domus Medica of the Faculty of Medicine, UiO, and five groups are located at OUS (Rikshospitalet). One group is located at the Faculty of Mathematics and Natural Sciences, at the Institute of Molecular Life Sciences.

STAFF AND RECRUITMENT

The Centre currently consists of 11 research groups as it did at its start-up in 2002, but the number of persons affiliated with the Centre has grown and has now passed 200 (including part-time positions). A large number of young and talented students have been recruited, many from abroad. Some 40 % of our staff comes from countries other than Norway. It should be noted that the Research Curriculum at the Faculty of Medicine ("Forskerlinjen") has been instrumental in securing a good recruitment base for the Centre. Examples of successful recruitments are EMBO long-term postdoctoral grants and Top Young Scientist Award in Europe for molecular biology granted by GE Healthcare together with the journal Science. In its recruitment efforts, CMBN has focused on establishing its own graduate-level researcher school, courses for researchers where students earn study credits, and a new series of international conferences. Several postdoctoral fellows have been recruited from prominent universities such as Yale, Cambridge, UC Berkeley and Oxford. Furthermore, a number of CMBN postdocs and young PIs have been recruited to prominent universities and frontline industry. The gender perspective is well balanced.

CMBN FUNDING

The CoE/SFF core funding from RCN makes up 15-20% of the total funding of the Centre.

The distribution of the different sources of income to the Centre for the period 2003 to 2012 is as follows:

- Own contribution (host institution/active partner): 25 %
- CoE funding (the RCN): 15-20 %
- Other external projects: 50-55 %

The total CMBN budget of external funding and host institution support has in 2003-2012 amounted to 80-130 MNOK per year.

35 % of the RCN funding has been allocated to CMBN common strategic investments, prioritized and agreed upon by the Steering group. Such infrastructure investments have been advanced equipment with dedicated expert-trained personnel and consumables, meetings, one year salaries for new PIs ("ventelønn"), etc.

Contributions of the host institutions UiO and OUS to CMBN:

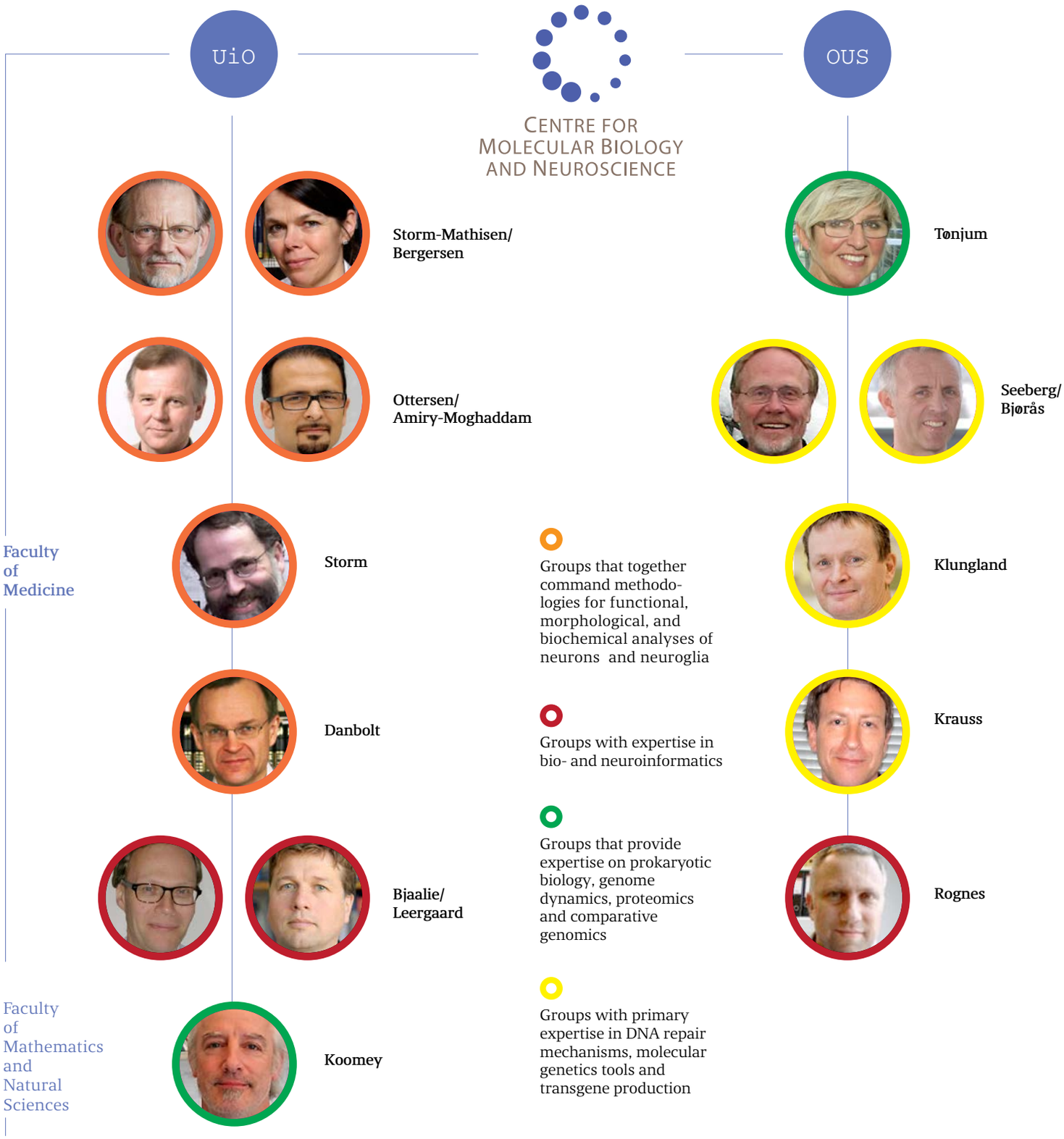
- UiO 2003-2012: 4 mNOK per year and administrative support
- OUS: 2 full permanent research positions.

	UiO funding	CoE funding	Other funding	Sum
2003	4 000	23 010	72 209	99 219
2004	4 000	21 175	57 017	82 192
2005	4 000	21 183	74 482	99 665
2006	4 000	21 193	68 214	93 407
2007	4 000	21 203	89 227	114 430
2008	4 000	21 211	95 400	120 611
2009	4 000	20 805	98 212	123 017
2010	4 000	20 700	102 800	127 500
2011	4 000	20 700	105 500	130 200
2012	4 000	18 820	113 041	133 693
Total	**40 000**	**210 000**	**772 102**	**1 126 102**

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!** --



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Tønjum Group
Genome Dynamics and Pathogenesis

Professor Tone Tønjum

ABOUT

The objective of our research is to highlight key aspects of molecular medicine with emphasis on the role of genome instability and maintenance in the pathogenesis of brain disease including infections. *We address cellular responses in CNS pathogenesis of meningitis, aging and Alzheimer's disease in humans and mice models, fuelled by the impact of genome instability and maintenance in health and disease.* These issues we pursue through the characterization of genome dynamics, molecular motors and membrane proteins in pathogenesis. We also use *microbes as models for eukaryotic systems in the search for novel diagnostics, prevention and therapeutics.*

RESEARCH FOCUS

Mechanisms for frequent genome variation, adaptation and maintenance are a necessity to ensure cellular fitness and survival in changing environments, for microbes and brain cells alike. Our main scientific goals are: (1) To understand the structure-function relationships and evolution of transformation of DNA. (2) To dissect how genome dynamics affect DNA sequence variability and conservation and thereby influence cellular fitness for survival and pathogenesis. (3) To develop new strategies for early diagnostics, prevention and treatment of disease. Addressing these topics in major pathogens, model bacteria and eukaryotic cellular systems as well as human clinical materials is most important for understanding the balance between fitness for survival and disease development. Our group focuses on these challenges in molecular medicine through translational research well integrated into strong local and international networks.

In order to dissect the molecular machine driving transformation of DNA, we have identified DNA binding components contributing to the DNA uptake sequence (DUS) and pilus-dependent neisserial transformation system. We hypothesize that transformation is directly coupled to pilus retraction, and that DNA is taken up into the cell in the wake of the retracting pilus. We have identified a number of novel DNA binding components and defined how they act and interact. In the search for the putative DUS-specific DNA binding receptor, we have subjected sub-cellular fractions to affinity-based assays to detect DNA binding proteins. Thereby, we have identified a number of novel DNA binding components and defined how they act and interact. Through deconstructing the meningococcal transformation machinery and searching for DNA binding components, we have also identified novel vaccine candidates.

We are also elucidating the effect of defects in DNA repair on cellular fitness and host defence, as well as virulence in a new meningitis mouse model. The effects of meningococcal brain infection on inflammation, water homeostasis and brain edema is striking. Also, the role of single nucleotide polymorphisms (SNPs) in DNA repair genes in brain aging and cognitive performance is addressed in healthy human cohorts as well as in well-defined patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD), providing new insight into genetic predisposition for disease.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

Our group has a number of discoveries and findings relating to the CMBN vision and subgoal V1: "The Centre shall take on a leading role in elucidating the role of DNA repair and genome maintenance mechanisms in preventing neurological disease and brain aging."

Firstly, we have discovered the conservative nature of transformation of DNA in neisserial evolution (Davidsen & Tønjum, ***Nature Microbiol Rev*** 4:11-22, 2006). We have shown that the abundant neisserial DNA uptake sequence (DUS) is biased towards 3R genes which therefore are preferentially taken up (Davidsen et al, ***Nucl Acids Res*** 32:1050-8, 2004), that DUS arise and perpetuate through recombination and not

mutation (Treangen et al, ***Genome biology*** 9:2 (R60), 2008), and defined the true identity of the neisserial DUS as a 12mer (Ambur et al, ***J Bacteriol*** 189:2077-2085, 2007). In this context, transformation is the bacterial process which is homologous to recombination in eukaryotic sex. We have shown that the efficiency of transformation is subject to antagonistic forces such as the DUS as a positive mediator while DNA restriction is a limiting factor (Ambur et al, ***PloS One*** 7:e39742, 2012),

Secondly, we have identified a number of novel DNA binding proteins including PilQ, PilG, and ComL relevant for transformation and processing of DNA (Assalkhou et al., ***Microbiol*** 153:1593-603, 2007; Lång et al, ***Microbiol*** 155: 852-62, 2009; Benam et al, ***Microbiol*** 157: 5, 1329-42, 2011). Notably, we have shown that DNA is bound in the central core of the PilQ macromolecular complex (Assalkhou et al, ***Microbiol*** 153:1593-1603, 2007), compatible with the model that both pili and DNA pass through the PilQ pore.

Both the DNA repair and antimutator role of bacterial MutY, MutS and Fpg have been assessed (Davidsen & Tønjum, ***Nature Micro Rev*** 4:11-22, 2006; Davidsen et al, ***J Bacteriol*** 187:2801-9, 2005; Davidsen et al, ***J Bacteriol*** 189: 5728-37, 2007; Tibbals et al, ***BMC Microbiol*** 9:7, 2009), showing that not all bacteria conform with the *Escherichia coli* paradigm. Through comparative genomics, the gene content in different bacterial species was shown to vary immensely, reflecting niche preferences (Ambur et al, ***FEMS Microbiol Rev*** 33: 453-470, 2009). Site-directed mutants have been constructed and naturally occurring clinical variants assessed to define the DNA repair profiles of clinical disease-associated isolates in *Neisseria meningitidis* (Davidsen et al, ***FEMS Immunol Med Microbiol*** 49:243- 251, 2007). Recently, these studies have been extended to the major pathogen *Mycobacterium tuberculosis* and the role of helicases in recombination has been assessed with a major focus on RecG, DinG and XPB (Balasingham et al, ***PloS One*** 7(5):e36960, 2012; Olsen et al, ***FEMS Immunol Med Microbiol*** 56:151-161, 2009; Zegeye et al, ***Microbiol*** 158:1982-1993, 2012). Assessing the evolution and diversity of clinical strains, *M. tuberculosis* residing in genetic isolation was was found to have twice as many SNPs in 3R genes as in other house-keeping genes, fuelling its evolution (***PloSOne*** 3(2):e1538, 2008).

Thirdly, addressing the human host and genetic predisposition for disease, we have monitored genome instability in human cohorts (meningitis, normal ageing and AD patients) and in mice models (Davidsen et al, ***Neuroscience*** 145:1375-87, 2007; Bohr et al, ***Neuroscience*** 145:1183-1186, 2007; ***Mech Age Dis*** 132:449-58, 2011). We hypothesize that impaired DNA repair and amyloid processing mechanisms may be predisposing factors for ageing-related brain changes and thereby constitute risk factors for AD. Only in the genes encoding DNA glycosylase hOGG1, AP endonucleaseI ApeI and the CXGD aspartate peptidase presenilin 1, healthy volunteers displayed nsSNPs that correlated with reduced cognitive performance, while all other genes were conserved, indicating that polymorphism in these DNA repair and presenilin genes may play a role in ageing-related cognitive decline (Lillenes et al., ***Mech Age Dev*** 132:449-58, 2011).

We have adressed subgoal V4 of the CMBN proposal in detail: "The Centre will further develop world-class expertise within microbial pathogenesis related to human disease in general and neurological disease in particular." Our studies of structure-function relationships of membrane proteins involved in the neisserial pilus biogenesis and transformation molecular machine encompass:

- Function and 3D structure of the macromolecular complex PilQ, including its orientation in the membrane (Collins et al, ***J Bacteriol*** 185:2611-7, 2003; Collins et al, ***J Biol Chem*** 279:39750-6, 2004; Frye et al, ***Microbiol*** 152:3751-64, 2006; Berry et al, ***PloS Pathogen*** 2012).

- PilQ-pilus interactions induce a conformational change in PilQ structure (Collins et al, ***J Biol Chem*** 280(19):18923-30, 2005; Berry et al, ***PloS Pathogen*** 2012), PilQ complex-lipoprotein PilP interactions (Balasingham et al, ***J Bacteriol*** 189:5716-27).

Deconstruction of the neisserial DUS and defining the biological activities of DUS dialects in related species (Frye et al, ***PloS Genetics*** 2013) are in process. The genome-wide effects of transformation, mutation and phase variation in *Neisseria meningitidis* (Davidsen & Tønjum, ***Nature Microbiol Rev*** 4:11-22, 2006, Alfsnes et al, ***mBio***, pending revision), cellular response to meningococcal meningitis and the immunoprotective potential of the PilQ complex (Collins et al, ***J Biol Chem*** 279:39750-6, 2004; Frye et al, ***Microbiol*** 152:3751-64, 2006; Berry et al, ***PloS Pathogen*** 2012) are still ongoing.

CMBN sub-goal V5 states that: "As spin-offs from its research activities, the Centre will deliver diagnostic and bioinformatics tools of considerable socio-economic and potential commercial value." Besides hypothesis-driven basic research, my laboratory has a keen interest in advanced state-of-the-art infrastructure and technology development and implementation as well as clinical diagnostics with access to vast amounts of clinical materials. A number of diagnostic and preventive measures are therefore added value from our basic science program (Balasingham et al, ***Mol Diagn Ther*** 13:137-51, 2009). We have also identified novel biomarkers for cognitive performance (Lillenes et al, ***Mech Age Dev*** 132:449-58, 2011) and AD (***ICAD*** 2012).

Finally, CMBN subgoal V6 highlights that: "The Centre will take on a primary responsibility for postgraduate teaching in the research field at the crossroads between molecular biology, genetics and neuroscience." In our group, we are deeply committed to contribute to a strong teaching environment at various levels, which also is a prerequisite to make an excellent research environment outstanding.

5 SELECTED PUBLICATIONS

I. Davidsen T, Rødland EA, Lagesen K, Seeberg E, Rognes T, Tønjum T. Biased distribution of DNA uptake sequences towards genome maintenance genes. Nucleic Acids Res 32:1050-8, 2004.

This paper demonstrates the fundamental discovery that DNA uptake by transformation preferentially mediates genomic conservation rather than variation. Representing a paradigm shift in evolutionary perception on the predominant outcome of transformation, a significant bias in the presence of the abundant DUS sequences inside genes towards 3R genes is detected, enabling them to be preferentially taken up, as a means of repair of DNA after genotoxic stress, followed up in Treangen et al, ***Genome biology*** 9:2 (R60), 2008.

II. Ambur O.H., SA Frye, T Tønjum. A new functional identity for the DNA uptake sequence in transformation and its presence in transcriptional terminators. J Bacteriol 189:2077-2085, 2007

Genome scanning for DUS occurrences in *Neisseria* species demonstrated that 76% of the nearly 2,000 neisserial DUS were found to have two semiconserved base pairs extending from the 5′ end of DUS to constitute a 12-mer repeat. The 12-mer was found to outperform the 10-mer DUS in transformation efficiency. Furthermore, half of the 1,500 12-mer DUS are arranged as inverted repeats predicted to be involved in rho-independent transcriptional termination. A similar distribution of the uptake signal sequence required for transformation in *Pasteurellaceae* was discovered. Therefore, we propose that the 10-mer identity of DUS should be recognized as a 12-mer. The dual role of DUS in transformation and on RNA affecting transcription makes this a relevant model system for assessing significant roles of repeats in biology.

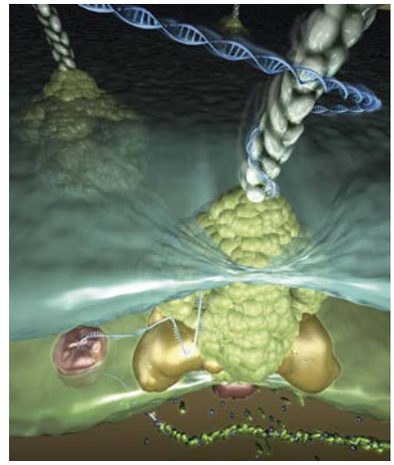

Fig. 1. *The molecular transformation machine. DNA is transferred into bacteria linked to the molecular machine that also performs pilus biogenesis, that spans the two cellular membranes. We suggest that transformation is directly coupled to pilus retraction, and that DNA is taken up into the cell in the wake of the retracting pilus. Recombination proteins then process and integrate DNA by homologous recombination (Nature Microbiol Rev. 4:11-22, 2006).*

III. Ambur OH, Frye SA, Nilsen M, Hovland E, T Tønjum. Restriction and sequence alterations affect DNA uptake sequence-dependent transformation in Neisseria meningitidis. PLoS One 7(7):e39742, 2012

Here we show that the efficiency of transformation is subject to antagonistic forces such as the DUS as a positive mediator while DNA restriction is a limiting factor. Manipulation of the transforming DNA allowed for quantifying the impact of three different mediators of meningococcal transformation: *Nla*IV restriction, homologous recombination and the DUS. An inverse relationship between the transformation frequency and the number of *Nla*IV restriction sites in DNA was observed when the transforming DNA harboured a heterologous region. In contrast, a particularly potent positive driver of transformation are the short DUS in the transforming DNA. Increasing the number of DUS in the transforming DNA was shown to exert a positive effect on transformation, which is depenedent on RecA-mediated homologous recombination.

IV. Balasingham SV, Zegeye ED, Rossi ML, Homberset H, Lærdahl JK, Bohr VA, T Tønjum. Enzymatic activities and DNA substrate specificity of Mycobacterium tuberculosis DNA helicase XPB. PloS One 7(5):e36960, 2012

We propose that helicases play a fundemantal role in *M. tuberculosis* genome instability, antigeic variation and drug resistance development. The helicase gene *ercc3/xpb* was found in *M. tuberculosis* but not *E. coli.* In addition to its DNA binding and unwinding activity assessed in a wide substrate profile, the expressed *M. tuberculosis* Ercc3-homolog XPB possessed intrinsic strand annealing activity.

V. Lillenes MS, Espeseth T, Støen M, Lundervold AJ, Frye SA, Rootwelt H, Reinvang I, T Tønjum. DNA base excision repair gene polymorphisms modulate human cognitive performance and decline during normal life span. Mech Age Dev 132:449-58, 2011

In a human normal aging cohort of 715 individuals, the genes encoding DNA glycosylase hOGG1 and AP endonucleaseI ApeI displayed nsSNPs that correlated with reduced cognitive performance. The findings support the hypothesis that polymorphisms in these DNA repair genes may play a role in ageing-related cognitive decline.

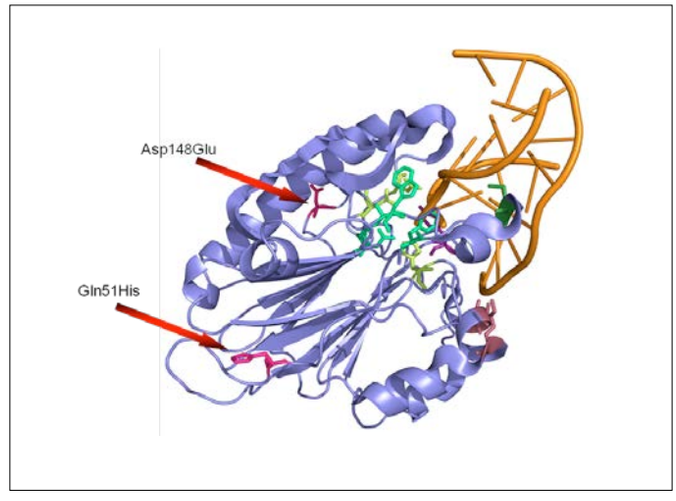

Fig. 2. Schematic diagram of the predicted 3D structure of the AP endonuclease ApeI *with the SNPs* $APE1_{Gln51His}$ *and* $APE1_{Glu148Asp}$ *highlighted (Mech Age Dev 132: 449-58, 2011).*

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Storm-Mathisen/ Bergersen Group Neurochemistry

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 energy metabolism for the function of gray and white matter. These mechanisms are studied in normal and pathological conditions, and during ontogenetic development and ageing, collaborating in-house and internationally at the gene repair / neuroscience intersection.

Brain and muscle energy group: Linda H. Bergersen Neuro- and gliotransmitters group: Vidar Gundersen Associated biotek group: Farrukh A. Chaudhry

RESEARCH FOCUS

Research by our group 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 signaling 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.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

The CMBN was established by the Research Council of Norway as a Centre of Excellence, based on the vision of combining the participants' unique "*expertise on DNA repair and neuroscience to address the role of DNA damage and repair in the pathogenesis of neurological diseases.*" (Application 11 Jan 2002)

Our research addresses the following work packages (WPs) of the CoE application 2002:

WP-1: *Brain and stem cell responses to DNA damage and the elucidation of novel repair genes and mechanisms (Vision1)*

WP-2: *Ageing, DNA repair and brain function (Visions 1 and 2).*

WP-3: *Dynamics of transport ... potential for therapy targeted to glutamate systems (Vision 2)*
Work task include

- Localization and quantification of the various transporters ... during development, adult life and ageing
- Function of metabolite transport
- Co-transmitters at glutamatergic synapses

***WP-4**: Regulation of synaptic transmission and postsynaptic integration in the normal, diseased and ageing brain (Vision 2)*

***WP-5**: Analysis and manipulation of cortical / hippocampal development and functions – relevance for targeted tissue repair (Visons 2 and 3).*

The recent papers by Bergersen in collaboration with the groups of Bjørås (Regnell et al ***Cell Rep*** 2012) and Klungland (Lauritzen KH et al ***Mol Cell Biol*** 2010; ***DNA Repair (Amst)*** 2011) epitomize the overarching CBMN goal of bringing together research on neuroscience and gene repair mechanisms, and to address the roles of DNA repair and damage in the pathogenesis of neurological diseases. These papers address ***WPs 1,2,3,5*** (See next page, and description under Publication I.)

The main focus of our research is on dynamics of transport of transmitters, co-transmitters and metabolites, eg lactate, at glutamatergic synapses ***WP3***, and on regulation of synaptic transmission ***WP4***. These themes are addressed by the papers mentioned under SELECTED PUBLICATIONS and Detailed achievements.

Detailed achievements: The ultrastructural localization of monocarboxyltate transporters (MCTs) (***Exp Brain Res*** 2001, ***Cereb Cortex*** 2005, ***Neuroscience*** 2007a) and identification of their role in temporal lobe epilepsy (***Neurobiol Dis*** 2011, 2012, ***Glia*** 2012), as well as in sustaining myelin structure and function (***J Neurosci*** 2011), and protecting cardiac muscles from ischemic damage (***Life Sci*** 2009) through lactate transport provides new approaches to understanding brain function and developing new therapy in brain diseases. Following the molecular identification of the glutamine transporter family (***Cell*** 1999, several subsequent papers), a role of glutamine has been defined for normal synaptic function (***J Neurochem*** 2008) as well as for dendritic retrograde signaling (***Cereb Cortex*** 2009c), and a potential target uncovered in Alzheimers

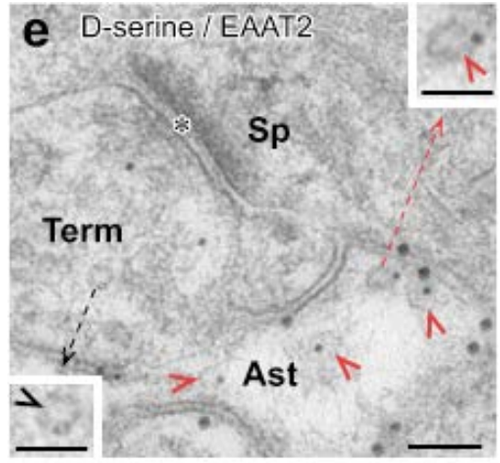

Fig. 1 Gial glutamate / D-serine co-transmission. *An astrocyte process (Ast) has synaptic-like microvesicles (red arrowheads) containing D-serine (small particles), and are separately shown to contain glutamate; the Ast is identified as having glutamate transporter EAAT2 in its plasma membrane (large particles) and is adjacent to a nerve ending (Term) synapsing on a dendritic spine (Sp). *, synaptic cleft. Bars 100 nm and 50 nm (insets). From: Bergersen et al 2012 Cereb Cortex [ISI Impact Factor 6.8]*

disease (***Neurochem Res*** 2008). 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). Astrocytes in several brain regions contain synaptic-like microvesicles with VGLUTs (***Glia*** 2012ab), and glutamate as well as the NMDA receptor modulator D-serine (***Cereb Cortex*** 2012b). The observations that even non-neural cells (***J Cell Sci*** 2004, ***J Lipid Res*** 2007, ***PLoS One*** 2011) 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, such as GABA (***Eur J Neurosci*** 2003, ***Molec Neurosci*** 2004, ***Cereb Cortex*** 2009a) and ATP (***Cereb Cortex*** 2012a), can be coreleased from nerve endings, 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 mtDNA and neuronal impairment including reduced size of synaptic contacts (Mol ***Cell Mol*** 2010, ***DNA Rep*** (Amst) 2011). Lack of the DNA repair enzyme Niel3 causes impaired synaptic structure and memory (***Cell Rep*** 2012).

5 SELECTED PUBLICATIONS

PubMed lists 84 publications from SN-Lab during the CMBN period. We have selected 5 recent important publications, representing 5 lines of research, and mention additional relevant illustrative papers by the group.

I. Regnell CE, Hildrestrand GA, Sejersted Y, Medin T, Moldestad O, Rolseth V, Krokeide SZ, Suganthan R, Luna L, Bjørås M, Bergersen LH. Hippocampal adult neurogenesis is maintained by Neil3-dependent repair of oxidative DNA lesions in neural progenitor cells. *Cell Rep* 2012 2:503-10.

Published in the new ***Cell*** series journal, with *Bergersen* and her PhD students (Regnell, Medin) as last and first authors in collaboration with the *Bjørås group*, this paper shows that the DNA glycosylase Neil3 is required for maintenance of hippocampal neural stem/progenitor cells and for normal memory and fear. Neil3(-/-) mice show age related impairment in synaptic structure and receptor density. Comparable but different changes were observed in collaboration with the *Klungland group*, in which expression of the mutated mtDNA repair enzyme mutUNG1 was induced to create a mouse model mimicking age related changes in the hippocampus (Lauritzen KH et al ***Mol Cell Biol*** 2010; ***DNA Repair (Amst)*** 2011).

II. Larsson M, Sawada K, Morland C, Hiasa M, Ormel L, Moriyama Y, Gundersen V. Functional and anatomical identification of a vesicular transporter mediating neuronal ATP release. *Cereb Cortex*. 2012 22:1203-14. [ISI Imp Fact 6.8]

Gundersen with his postdoc Larson as first author and two PhD students (Morland, Ormel) collaborated with a *Japanese* team to identify the organelle and molecular basis for the role of ATP as neurotransmitter. This continues a series of studies discovering novel aspects of neurotransmitter storage in vesicles: vesicular glutamate transporter VGLUT3 identified (Fremeau et al ***PNAS*** 2002); developmental dynamics of

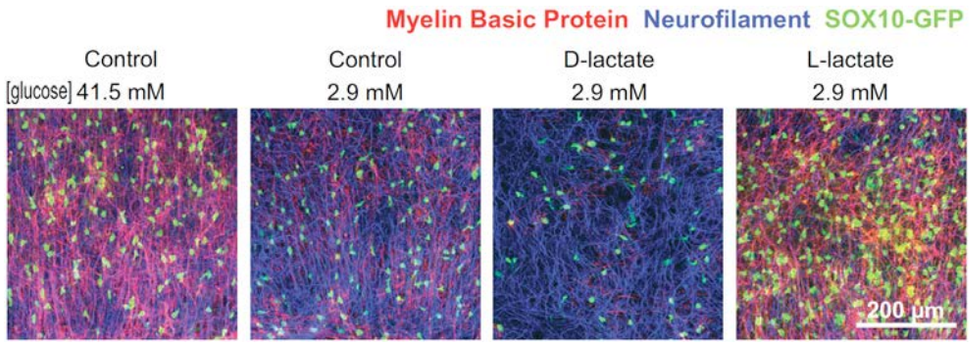

Fig. 2 L-lactate supports survival of oligodendrocyte linage cells (SOX10-GFP) and their formation of myelin (MBP) around nerve fibres (Neurofilament). D-lactate suppresses. (A). From: Rinholm et al *J Neurosci* 2011 [IF 7.1]

VGLUT1-3 (Fremeau et al ***Science*** 2004; Boulland et al ***J Comp Neurol*** 2004); dendritic retrograde signaling by VGLUT3 (Harkany et al ***J Neurosci*** 2004); vesicular GABA at excitatory synapses (Bergersen et al ***Eur J Neurosci*** 2003); release of aspartate from GABAergic neurons (Gundersen et al ***Mol Cell Neurosci*** 2004); re-organization of VGLUT1 and VGAT in epilepsy (Boulland et al ***J Comp Neurol*** 2007); neuronal sorting of vesicles with VGLUT2 and VGAT (Boulland et al ***Cerebr Cortex*** 2009); synapsin dependent vesicular dynamics at a glutamatergic synapse (Owe et al ***Cereb Cortex*** 2009); novel roles of vesicular glutamate transport in insulin secreting granules (Gammelsaeter et al ***PLoS One*** 2011), vesicular co-localization of VGLUT3 with GABA or acetylcholine in select neuronal populations (***J Comp Neurol*** 2013, atlas online at http://www.bwb.org).

III. Bergersen LH, Morland C, Ormel L, Rinholm JE, Larsson M, Wold JF, Røe AT, Stranna A, Santello M, Bouvier D, Ottersen OP, Volterra A, Gundersen V. Immunogold detection of L-glutamate and D-serine in small synaptic-like microvesicles in adult hippocampal astrocytes. *Cereb Cortex* 2012 22:1690-7. [ISI Imp Factor 6.8]

Gundersen, Bergersen and 7 other group members worked with a group in *Switzerland*. They show the structural basis for D-serine/glutamate corelease (Fig. 1) activating NMDA-type glutamate receptors. Two earlier shared first and last authorship papers showed astrocytes to have microvesicles exocytosing glutamate, similar to synaptic vesicles releasing transmitter from nerve endings (Bezzi et al ***Nat Neurosci*** 2004), and that this serves to boost synaptic transmission (Jourdain et al ***Nat Neurosci*** 2007). Such glio-transmission appears to be general (Bergersen, Gundersen ***Neuroscience*** 2009; Ormel et al ***Glia*** 2012 Feb; Ormel et al ***Glia*** 2012 Sep). A novel aspect of this line of research is the discovery of microglial fine processes contacting synapses in the cerebral cortex (***Eur J Neurosci*** 2013).

IV. Lauritzen F, Heuser K, de Lanerolle NC, Lee TS, Spencer DD, Kim JH, Gjedde A, Eid T, Bergersen LH. Redistribution of monocarboxylate transporter 2 on the surface of astrocytes in the human epileptogenic hippocampus. *Glia.* 2012 60:1172-81. [ISI Impact Factor 5.2]

Bergersen with her PhD student (F. Lauritzen) have a series of papers in which they utilize the unique material of human epileptic hippocampus available at *Yale University* as well as rat models of temporal lobe epilepsy (Lauritzen F et al ***Neurobiol Dis*** 2001 & 2012; Perez et al ***Neurobiol Dis*** 2012). They show selective redistributions of proteins, including the monocarboxylate transporters MCT1 and MCT2, indicating causative changes of lactate and energy supply in epilepsy. Bergersen pioneered the EM localization of MCTs (Bergersen ***Neuroscience*** 2007 review) and discovered that MCT2 in rat brain concentrates at excitatory postsynaptic membranes (Bergersen et al ***Exp Brain Res*** 2001; ***Cereb Cortex*** 2005) indicating signaling as well as metabolic roles of lactate. This theme is followed up with colleagues at the *University of Copenhagen* (Vafee et al ***J Cereb Blood Flow Metab*** 2012; Bergersen, Gjedde ***Front Neuroenergetics*** 2012).

V. Rinholm JE, Hamilton NB, Kessaris N, Richardson WD, Bergersen LH, Attwell D. Regulation of oligodendrocyte development and myelination by glucose and lactate. *J Neurosci* 2011 31:538-48. [ISI Impact Factor 7.1]

Bergersen, shared last author, her student Rinholm and a group at the *University College London* show that myelin formation requires lactate (Fig. 2). With the London group, Bergersen earlier discovered NMDA receptors on oligodendrocytes, which make myelinated nerve tracts prone to damage (Káradóttir et al ***Nature*** 2005). Her EM expertise got the latter paper accepted and prompted a methods review (Bergersen et al ***Nat Protoc*** 2008). She was asked to comment on other roles of lactate in oligodendrocytes (Rinholm, Bergersen ***Nature*** 2012).

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Amiry-Moghaddam/ Ottersen Group Laboratory Of Molecular Neuroscience

Professor Mahmood Reza Amiry-Moghaddam

Professor Ole Petter Ottersen

ABOUT

The research at the Laboratory for molecular neuroscience has been focused on molecular mechanisms involved in the development of acute and chronic neurodegenerative diseases. It has aimed at unraveling the molecular basis for cell death and edema development in stroke and other neurological conditions, and explored 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.

RESEARCH FOCUS

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.

Unraveling the molecular mechanisms underlying brain edema, epilepsy and neurodegenerative diseases, such as Alzheimer's disease, has been a major focus of the research in our laboratory.

In the past 10 years, several of our projects havefocused on the physiological and pathophysiological roles of water channel molecules (aquaporins) in brain. The membrane domain specific expression of the brain aquaporin, AQP4, was first demonstrated by our group in 1997 (Nielsen, Nagelhus et al 1997). Since then we have unraveled the role of this molecule in formation of brain edema and as a novel drug target in treatment of early post-stroke and hyponatremic edema.

Exploring the role of astrocytes in the pathophysiology of neurological conditions such as mesial temporal lobe epilepsy, Parkinson's disease and Alzheimer's disease has been another focus of our research.

In the case of Alzheimer's disease we have investigated the dynamics of beta-amyloid deposition in relevant animal models.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

Our group made a major breakthrough already in the first year with CoE status. By use of a membrane domain specific knockout strategy we could identify a pool of water channels (aquaporin-4, AQP4) that control water influx in experimentally induced brain edema. The results (published in PNAS, 2003) drew editorial comments in ***Nature Reviews Neuroscience*** (portrayed as "Highlight") and prompted an invitation to write a review for the same journal. This review (Amiry-Moghaddam & Ottersen, ***Nature Reviews Neuroscience*** 2003) stands as a landmark paper in the field, judged by the high number of citations (>270 to date).

Several new discoveries followed in the wake of the 2003 study mentioned above. Research on water channels in brain developed into a major activity of the group and led to a number of articles in top tier journals, including seven papers in the Proceedings of the National Academy of Sciences USA (***PNAS***). Loss of AQP4 from endfeet was demonstrated in brain ischemia (explaining the persistence typical of post-stroke edemas), and a molecular complex was identified that could serve as the elusive glial osmosensor. Specifically, the latter complex (consisting of AQP4 and transient receptor potential vanilloid channel 4; TRPV4) was found to be responsible for translating osmotic challenges into regulatory volume adjustments (Benfenati et al., ***PNAS***

2011). These findings have important implications for our understanding of how neural cells – and the brain as a whole - maintain an adequate volume homeostasis in physiological and pathophysiologcial situations.

Our studies on water channels also led to new concepts as to the structure and function of the blood-brain-barrier. 3D reconstruction analyses revealed that astrocytic endfeet form a continuous sheath around brain capillaries, while a new glial-conditional AQP4 knockout generated in our laboratory demonstrated that the pool of AQP4 – shown in 2003 to control water influx in brain – indeed resides in astrocytes (Haj-Yasein et al., ***PNAS*** 2011). Taken together, these findings of ours indicate that the perivascular glial sheath assumes barrier function to water transport in pathophysiological conditions. Our data will require modifications to the textbook account of the blood-brain-barrier.

Taken together, our work conducted during the CMBN funding period has led to fundamental new insight in the molecular mechanisms underlying water transport, edema formation, and cell volume control in brain. In addition, our projects have unraveled novel functions of glial cells and provided a better understanding of pathogenetic processes underlying epilepsy and Alzheimer's disease. Our group has published more than 100 papers in the period 2002-2012 and receives more than 1000 citations per year. This makes our group one of the most frequently cited neuroscience groups in the world, according to ISI Highly Cited Research (http://highlycited.com).

Work in our group has attracted much international interest (judged by citations and invitations to give keynote lectures) and is acknowledged through international prizes (including the Lundbeck Prize to Ottersen, and the Jahre Senior Prize and Jahre Prize for Young Investigators to Ottersen and Amiry-Moghaddam, respectively).

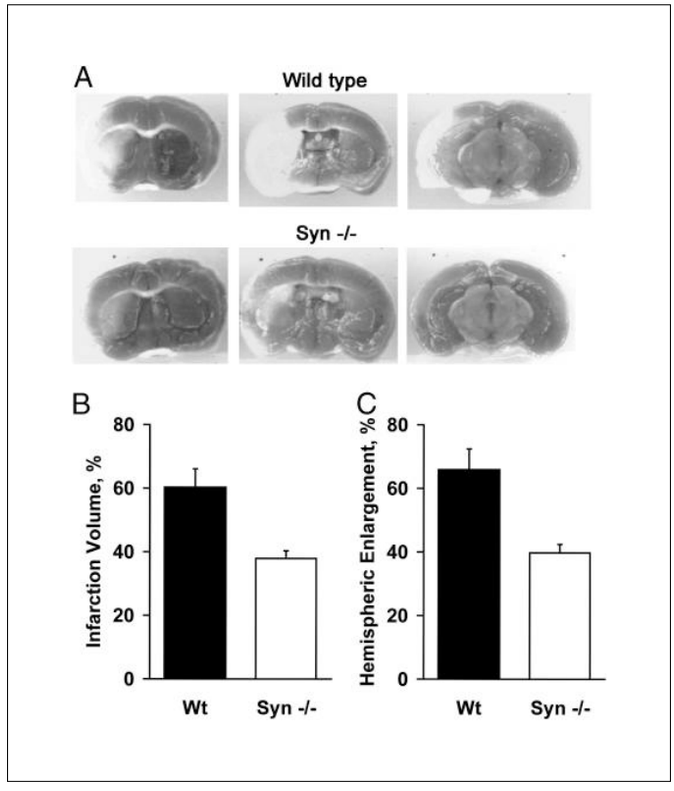
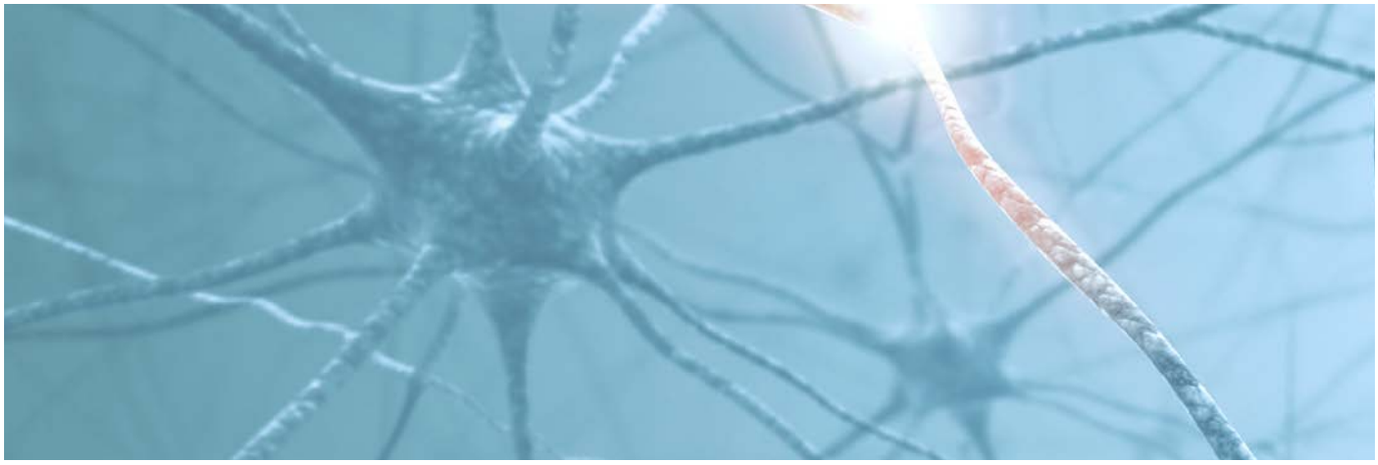


Fig. 1. *Mice with loss of the perivascular pool of AQP4 were achieved by genetic deletion of a-Syn, the protein responsible for anchoring of AQP4 at the perivascular astrocyte endfeet. Difference in brain injuries sustained by α-Syn−/− and WT mice after ischemia reperfusion. After 90 min of middle cerebral artery occlusion and 23 h of reperfusion, α-Syn−/− (n = 8) and WT (n = 9) mice were killed, and the brains were sectioned. Slices were incubated with triphenyltetrazolium chloride, and infarction volume and hemispheric enlargement were determined). (A) Corresponding serial brain sections reveal smaller infarct zone (unstained) in slices from α-Syn−/− mice compared to WT mice. (B) Quantification of infarction volumes determined by image analysis. (C) Determination of hemispheric enlargement. Brains of α-Syn−/− mice were partially protected (P < 0.05 for both parameters). From: Amiry-Moghaddam et al. PNAS 2003, 100(4): 2106-2111*



Our work has provided better understanding of a number of neurological conditions - including brain edema, epilepsy, Alzheimer's disease and other age related diseases - and has opened new avenues for treatment. This is in accord with the vision of the centre. Notably, the molecular underpinning of brain edema formation has been unravelled, and great strides have been made towards the generation of water channel blockers of therapeutical potential. Specifically, a cyclic peptide has been synthesized de novo that fits into an external binding site of the AQP4 molecule (Jacobsen et al., 2011). This peptide will serve as a scaffold for the engineering of pore blockers that promise to prevent water entry in conditions associated with brain edema. Further, and squarely within the scope of the Centre, DNA repair mechanisms have been elucidated in brain and brain ageing, drawing on the complementary competence of the CMBN groups. The vision – pursuing research from molecules to medicine – has been duly realized.

5 SELECTED PUBLICATIONS

I. Amiry-Moghaddam M, Otsuka T, Hurn PD, Traystman RJ, Haug FM, Froehner SC, Adams ME, Neely JD, Agre P, Ottersen OP*, Bhardwaj A. An alpha-syntrophin-dependent pool of AQP4 in astroglial end-feet confers bidirectional water flow between blood and brain. Proc Natl Acad Sci U S A. 2003, Feb 18; 100(4):2106-11.

This was the first functional analyses of the mice with targeted disruption of the anchoring protein responsible for the polarised expression of AQP4 at the perivascular astrocyte membranes. Here we showed that removal of perivascular aquaporin-4 offered partial protection against postischemic brain edema, suggesting that perivascular AQP4 constitutes an influx route for water in edema formation. This work was identified as a "Neuroscience Highlight" in ***Nature Reviews Neuroscience***.

II. Amiry-Moghaddam M, Williamson A, Palomba M, Eid T, de Lanerolle NC, Nagelhus EA, Adams ME, Froehner SC, Agre P, Ottersen OP. Delayed potassium clearance and increased seizure severity I mice lacking alpha-syntrophin. Proc Natl Acad Sci U S A. 2003 Nov 11; 100(23):13615-20

In this study we tested for a possible coupling between water and K+ transport in the brain. We investigated the dynamics of K+ clearance in alpha-syntrophin knockout mice (which lack perivascular aquaporin-4 and is a model for loss of astrocyte polarity). It was found that the knockout mice were impaired in their ability to clear extracellular K+ after orthodromic activation of hippocampal neuropil. These were the first data to support a coupling between water and K+ transport in the brain and raised the possibility that aquaporins, and astrocyte polarity might be indirectly involved in regulation of neuronal excitability. In agreement, in the same study, it was shown that the knockout mice developed more severe seizures than wild type mice in an experimental model of epilepsy. This study was the first to demonstrate a functional coupling between water transport and K+ clearance, and the first of a series of articles showing loss of astrocyte polarity as a common denominator of neurological disorders with defect water and K+ homeostasis.

III. Amiry-Moghaddam M and Ottersen OP. Molecular Basis for Water transport in Brain. Nature Reviews Neuroscience (2003) Dec 4:991-1001 (Invited review) Cited: >270 to date

Due to the international interest that my studies had received, we were invited by Nature Reviews Neuroscience to write a review on the role of aquaporins in brain water homeostasis. This review is one of the most highly sited reviews in this field.

IV. Benfenati V, Caprini M, Dovizio M, Mylonakou MN, Ferroni S, Ottersen OP, Amiry-Moghaddam M*. An aquaporin-4/ transient receptor potential vanilloid 4 (AQP4/TRPV4) complex is essential for cell-volume control in astrocytes. Proc Natl Acad Sci U S A. 2011 Feb 8;108(6):2563-8.

This paper represents a significant step forward in identifying the "volume regulating complex" in brain. Using several technical approaches such as protein chemistry, electrophysiology, molecular biology and immunofluorescence, we show that the water channel AQP4 and the cation channel TRPV4 are involved in a molecular complex involved in volume regulation in astrocytes. Specifically we show that both AQP4 and TRPV4 are necessary for the calcium response and the regulatory volume decrease (RVD) in astrocytes exposed to hypotonic stress. So far, most of the studies performed on AQP4 have focused on its role in the brain pathology. Our study is one of the first studies indicating a physiological role for the water channel AQP4 in the brain. This study sheds new light on the mechanisms involved in osmosensing and volume regulation in the brain.

V. 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. Proc Natl Acad Sci U S A. 2011 Jan 11;108(2):846-51. (Ottersen OP shared corresponding author) Critical role of aquaporin-4 (AQP4) in astrocytic Ca2+ signaling events elicited by cerebral edema. Comment in Nat Rev Neurosci. 2011 Feb;12(2):66.

In this study we provide evidence that brain swelling triggers Ca(2+) signaling in astrocytes and that deletion of the Aqp4 gene markedly interferes with these events. Using in vivo two-photon imaging, we show that hypoosmotic stress (20% reduction in osmolarity) initiates astrocytic Ca(2+) spikes and that deletion of Aqp4 reduces these signals. These results suggest that AQP4 not only serves as an influx route for water but also is critical for initiating downstream signaling events that may affect and potentially exacerbate the pathological outcome in clinical conditions associated with brain edema.

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Bjørås Group Laboratory for Molecular Biology

Professor Magnar Bjørås

ABOUT

The Bjørås group in CMBN focuses on: (i) Impact of oxidative DNA base lesion repair on ageing, and disease. (ii) Structural biochemistry of DNA base lesion repair. (iii) DNA repair and biological responses to DNA damage in microbial cells. (iv) Biogenesis and maintenance of mitochondrial DNA. (v) Model studies of DNA damage responses and cell cycle regulation in yeast. Challenges are to understand the mechanisms for cellular protection against DNA damage and its role in ageing, stem cell maintenance and disease (i.e. neurological disease and cancer).

RESEARCH FOCUS

The Bjørås group 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. Five postdocs/ senior researchers (Lars Eide, Ingrun Alseth, Bjørn Dalhus, Jorrit Enserink and Stig Ove Bøe) with support from the Bjørås group and CMBN have established their own research groups with their own funding during the last five years. A summary of all activities is presented below:

Impact of oxidative DNA base lesion repair in ageing and disease. During the last 10 years it has been a major activity of the Bjørås group to study the impact of DNA base lesion repair on various diseases such as neurological disorders, and cancer. In particular, we focus on the significance of oxidative DNA damage repair for neurodegeneration and cognitive function, including the importance of neurogenesis (neuronal stem cell proliferation and differentiation). Most of these projects include construction and analysis of DNA repair deficient mouse models, cell lines and/or patient samples. Ten different DNA glycosylase deficient mouse models have been generated since 2002. Of importance for translational research the Bjørås group has established several collaborations with clinical departments at OUS (e.g. Internal medicine; Pediatrics). In 2007, Stig Ove Bøe was recruited to the Bjørås group as a senior researcher to work on the role of the nuclear protein PML in acute promyelocytic leukemia (APL). In 2011, Bøe established his own research group at Department of medical biochemistry, Rikshospitalet. His main objective is to identify molecular mechanisms that underly the successful treatment of APL with ATO and ATRA and to assess if these therapeutic concepts can be generally applied to treatment of other types of cancers.

Structural biochemistry of DNA base lesion repair. To elucidate the molecular mechanisms for DNA base lesion repair proteins we have solved the atomic structure (3D) of several DNA-protein complexes. In 2007, the Bjørås group established a core facility for Structural biology and bioinformatics at OUS/ UiO to support researchers in the health region, HSØ (http:// core.rr-research.no/index.php? section=4). The facility has contributed to more than 30 publications since 2007. In January 2012, Bjørn Dalhus, which has worked as a postdoc/senior researcher in the Bjørås group from 2004 to 2011, replaced Bjørås as manager for the core facility and established his own research group Dep of medical biochemistry (Rikshospitalet). He is focusing on the structural biochemistry for recognition and removal of DNA base lesions and modifications.

DNA repair and biological responses to DNA damage in microbial cells. We have identified and characterized new DNA repair functions involved in base lesion repair in bacteria such as Bacillus, Mycobacterium and E. coli. Another important research project in the Bjørås group is to elucidate the function of small non-coding RNA and small peptides that modulate the response to DNA damage in *E. coli*. We have demonstrated proof of concept to use a highly toxic small inner membrane peptide from *E. coli*, to treat sepsis. This novel idea of antimicrobial treatment is patented and a start-up company (Qotics) established to further develop the concept.

Biogenesis and maintenance of mitochondrial DNA. Partly supported by the CMBN group of Bjørås, Lars Eide has specialized on mitochondrial function related to the integrity of mitochondrial DNA. In 2007, Eide obtained a permanent position (1. amanuensis/professor) and established his own group at Dep of medical biochemistry (Rikshospitalet). His group aims to understand how mtDNA integrity influences on the organization of the electron transport chain complexes in the mitochondrial membranes as well as regulation of aerobic/anaerobic metabolism in the mitochondria in association to metabolic disease and neurodegeneration.

Model studies of DNA damage responses and cell cycle regulation in yeast. Partly supported by CMBN, research scientist Ingrun Alseth has established an independent research group at Dep of microbiology during the five last years. Her research is focusing on yeast (*S. cerevisiae* and *S. pombe*) as a eukaryotic model organism for DNA base lesion repair. In 2008, Dr. Enserink was awarded the highly competitive Outstanding Young Investigator ('YFF', Yngre Fremragende Forsker) fellowship from the Norwegian Research Council and established his own research group at the Dep of microbiology at OUS. He has also been partly supported by CMBN. The major line of research in Enserink's group involves the model organism *S. cerevisiae*. His group focuses on the role of CDKs in cell cycle-regulated processes.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

The most important achievements by the Bjørås group in CMBN according to the visions (V) and the work packages (WP) in the CoE application:

V1. ***"The Centre shall take on a leading role in elucidating the role of DNA repair and genome maintenance mechanisms in preventing neurological disease and brain ageing" (WP 1 and 2).*** In collaboration with the Ottersen and the Krauss group we showed that most of the DNA glycosylases removing oxidative DNA damage were widely expressed in brain except Neil3 which was restricted to regenerative niches, subventricular zone and subgranular zone (Rolseth et al **DNA repair** 2008a**;** Rolseth et al **DNA repair** 2008b). The free radical theory of ageing and accumulation of oxidative DNA damage has been put forward as a potential cause for cognitive deficits. In order to address the biological significance of oxidative DNA damage repair we generated ten different mouse strains deficient in DNA glycosylases initiating repair of a broad range of oxidative DNA base lesions. In collaboration with Linda Bergersen we have demonstrated that the Neil3 DNA glycosylase is important for induced and adult neurogenesis (Hildrestrand et al **DNA repair** 2007; Sejersted et al **PNAS** 2011; Regnell et al **Cell Reports** 2012). Currently, we are investigating several of the other DNA glycosylase deficient mouse strains for cognitive performance, neurodegeneration, neurogenesis and accumulation of oxidative DNA damage. In collaboration with Cynthia McMurray and Arne Klungland we demonstrated that the Ogg1 and Neil1 DNA glycosylases promotes triplet expansion in Huntington disease (Kovtun et al **Nature** 2007; Møllersen et al **Hum Mol Gen** 2012). We demonstrated that the level of oxidative mitochondrial DNA damage determines neural stem cell differentiation fate (Wei et al **Stem Cells** 2010; Wei et al **J Neuroscience** 2010).

WP-1 "..elucidation of of novel repair genes and mechanisms". The group has been involved in identification and characterization of several novel DNA repair functions/mechanisms (Aas et al **Nature** 2003; Alseth *et al* **NAR** 2004; Alseth *et al* **NAR** 2005; Sundheim et al **EMBO** 2006; Alseth et al **Mol Micro** 2006; Dalhus et al **Nature SMB** 2009; Nilsen *et al* **NAR** 2011). A new line of research focuses on cell cycle cycle control by cyclin dependent kinases and the DNA damage response (Enserink et al **J Cell Biol** 2009; Zimmermann *et al* **PNAS**; 2012; Chymcowitch *et al* **PNAS** 2012)

WP-2"...DNA repair, cancer and ageing". We have several works focusing on the impact of DNA base lesion repair and the oncoprotein PML-RARA for cancer development (Forspring *et al* Carcinogenesis 2009; Isakson *et al.*, Blood 2010; Halsne *et al* DNA repair 2012; Lång *et al.*, Blood 2012).

V4. ***"The Centre will also further develop world-class expertise within microbial pathogenesis related to humane disease in general and neurological disease in particular (WP7)".*** We have identified and characterized DNA base lesion repair enzymes in several pathogenic bacteria (Åmodt *et al* **JBC** 2004; Alseth *et al* **Mol Micro** 2006; Mingyi *et al* **DNA repair** 2011) and virus (Aukrust et al **Blood** 2005; Ranneberg-Nilsen et al **Virology** 2006; Ranneberg-Nilsen *et al* **JMB** 2008; Ranneberg-Nilsen et al **PLoS One** 2012). In collaboration with Rognes we have identified and characterized the function of small non-coding RNA and small peptides that modulate the response to DNA damage in *E. coli* and other bacteria (Weel-Sneve *et al* **NAR** 2008; Thomassen *et al* **PLoS One** 2010; Sneve *et al* **PLoS Genetics**, 2012, pending revision).

V5 ***"As spin-offs from its research activities, the Centre will deliver diagnostic and bioinformatics tools of considerable socio-economic and potential commercial value (WP8)"***. We have demonstrated proof of concept to use a highly toxic small inner membrane peptide from *E. coli*, to treat sepsis. This novel idea of antimicrobial treatment is patented and a start-up company (Qotics) established to further develop the concept. We have identified compounds inhibiting DNA glycosylases or CDKs by structure-based-drug-design and chemical arrays. The most promising compounds are currently tested in cell based assays.

V6. ***"The Centre will take on a primary responsibility for postgraduate teaching in the research field at the crossroads between molecular biology, genetics and neuroscience (vide infra)".*** During the last five years five postdocs/senior researchers (Lars Eide, Ingrun Alseth, Bjørn Dalhus, Jorrit Enserink and Stig Ove Bøe) with support from the Bjørås group and CMBN have established their own research groups with their own funding at OUS and UiO.

5 SELECTED PUBLICATIONS

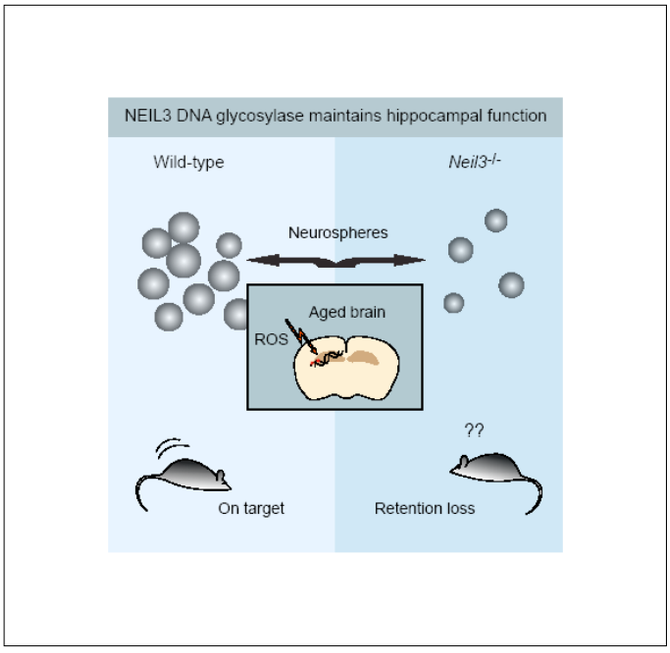
I. Kovtun, IV., Liang, Y., Bjørås, M., Klungland, A., Wilson, W. and McMurray, CT. OGG1 initiates age-dependent somatic CAG expansion during normal base excision repair of oxidized bases *in vitro* and *in vivo*. *Nature*, 447-52, 447 (2007)

II. Dalhus, B., Arvy, A., Rosnes, I., Alseth, I., Cao, W., Olsen, ØE., Tainer, J., Bjørås, M. Structural basis of repair of deaminated adenine in DNA by EndonucleaseV. *Nature SMB*, 16, 138-43 (2009)

III. Wang W, Esbensen Y, Kunke D, Suganthan R, Bjørås M, Eide L. Mitochondrial DNA Damage level determines Neural Stem Cell differentiation fate. *J. of Neuroscience* 31(26):9746-51 (2011).

IV. Sejersted Y, Hildrestrand GA, Kunke D, Rolseth V, Krokeide SZ, Gran CN, Suganthan R, Aasegg MA, Fleming AM, Saugstad OD, Burrows CJ, Luna L and Bjørås M. Stroke induced neurogenesis requires Neil3 DNA glycosylase. *PNAS* 108(46):18802-72011 (2011).

V. Regnell CE, Hildrestrand GA, Sejersted Y, Medin T, Moldestad O, Rolseth V, Krokeide SZ, Suganthan R, Luna L, Bjørås M, and Bergersen LH* Hippocampal adult neurogenesis is maintained by Neil3-dependent repair of oxidative DNA lesions in neural progenitor cells. *Cell Reports* (2012) Corresponding authorsprogenitor cells. Cell Reports (2012) *Corresponding authors



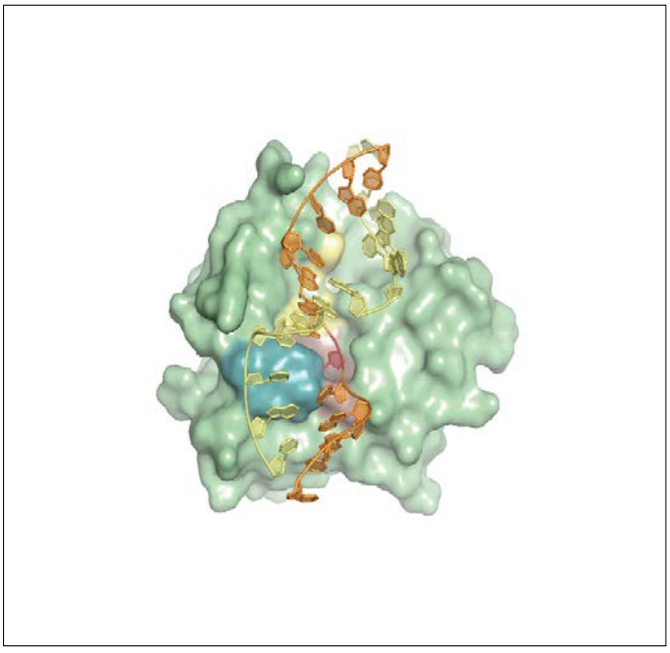


Figure 1. *Adult neurogenesis is crucial for maintenance of hippocampus-dependent functions involved in behavior. Herein, behavioral studies revealed learning and memory deficits and reduced anxiety-like behavior in Neil3$^{-/-}$ mice. Neural stem/progenitor cells (neurospheres) from aged Neil3$^{-/-}$ mice showed impaired proliferative capacity. Further, hippocampal neurons in Neil3$^{-/-}$ mice displayed synaptic irregularities. It appears that Neil3-dependent repair of oxidative DNA damage in neural stem/progenitor cells is required for maintenance of adult neurogenesis to counteract the age associated deterioration of cognitive performance. Regnell et al,* ***Cell Reports****, 2012.*

Figure 2. Molecular surface of Endonuclease V with bound DNA (orange and yellow tubes and rings) showing spatial relationships among key structural elements. *The strand-separating PYIP wedge (cyan, left) protrudes out adjacent to residues Asp43, Glu89, Asp110 and His214, which are involved in Mg2+ ion binding and phosphodiester incision (yellow, center). Also shown is the hypoxanthine lesion and the surrounding residues (Leu85, Gly111, Gln112, Gly113, Gly136 and Leu142) that form the nucleobase pocket (red, center). Dalhus et al,* ***Nature SMB,*** *2009.*

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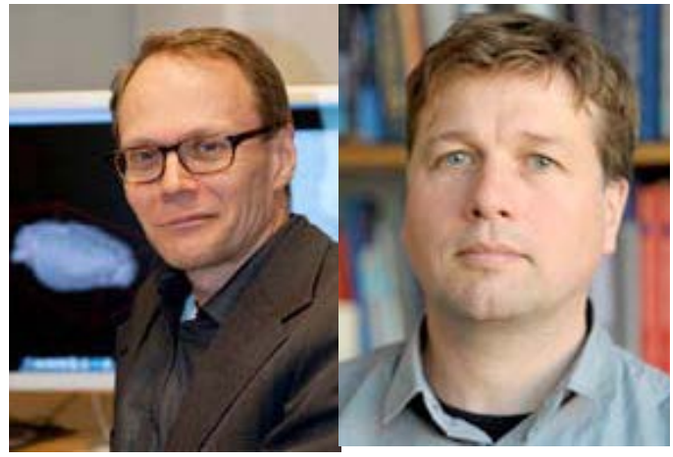

ABOUT

The areas of research covered by NeSys are computational neuroanatomy, neuroimaging, and neuroinformatics. The main aim has been to develop and implement new tools and technologies for analysis of brain architecture, connectivity, and gene and molecular distribution at the level of regions and whole brain. During the CMBN project period, the group has also established the first animal PET facility in Norway.

RESEARCH FOCUS

Much of the research carried out today on rodent models generates high resolution image data, allowing characterization and analysis of 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, we have developed data management systems and tools for analysis and visualization of brain architecture. Data accumulated in our systems and analyzed with accompanying suites of tools are used for both hypothesis driven as well as discovery based research.

Projects carried out in our group include

Neuroscience databasing and atlasing; data integration: Development of database applications and brain atlasing systems for image data from mouse and rat. The levels covered range from microscopy (gene and molecular distribution, connectivity, and general architecture) to in vivo imaging (PET/CT/MR).

Localization in the brain: Establishment of pipelines and workflows for studies of the localization of features in the brain, beginning with data production and ending with data storage, retrieval, and analysis. Our work has included development and/or integration of large scale data acquisition from microscopes (robotic microscopy / section scanning), computerized 3-D reconstruction and visualization, data management, and positioning of data in digital brain atlas systems.

Brain map transformations: Analysis of design principles for major circuits in the brain, including changes in the architecture following external and genetic manipulations.

High resolution MRI and microPET in mouse and rat: Use of state-of-the-art tomographic imaging techniques for analysis of structural and functional relationships in the brain following experimental perturbations or disease.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

Brain databasing and atlasing systems are key tools for data integration, showing how the different components of the brain, analysed at different levels of granularity, work together to perform various functions in health and disease. NeSys technology developments in this area thus represent a contribution to the CMBN vision of becoming one of the most innovative environments internationally for the identification, development and promotion of new approaches to the treatment of brain disease and age-related neurological impairment. Further, these developments have resulted in bioinformatics/ neuroinformatics tools of considerable socio-economic value, primarily through the systematic sharing of resources (including tools) via online services.

Towards this vision, we have established The Rodent Brain Workbench (www.rbwb.org) as a channel for dissemination of tools, data, and knowledge produced by our research group and global network of collaborators. Further, on partial leave of absence from CMBN, Jan Bjaalie contributed as founding Executive Director to the establishment of the International Neuroinformatics Coordinating Facility (INCF)

at Karolinska Institutet, an international organization devoted to development of infrastructures for neurosciences, including standards, guidelines and references for data sharing, modeling, and simulation (Bjaalie and Grillner ***J Neurosci*** 2007; Bjaalie Front ***Neurosci*** 2008). Services include a portal to neuroinformatics (www.incf.org), including the INCF Software Center (software.incf.org) for sharing of tools for neurosciences.

In the domain of digital brain atlasing, a key result is the 3-D reconstruction of the Paxinos Watson rat brain atlas delivered to the community as a shared tool, in agreement with the publisher (Hjørnevik et al ***Front Neuroinform*** 2007). This 3-D atlas has a large user base and allows flexible analysis of imaging data (PET, MR), exploited in several projects including analysis of structure-function relationships in disease models. Further, three categories of atlases have been developed:

Online atlas of detailed histological organization and definition of structures at the regional level: The Rat Hippocampal Atlas (Kjønigsen et al ***Front Neuroinform*** 2010)

Online atlas of brain-wide connectivity at the level of single barrels of the primary somatosensory cortex: The Whole Brain Connectivity Atlas (Zakiewicz et al ***PloS ONE*** 2010)

Online atlases of gene and molecular distribution for disease models and general brain mapping: TET-OFF atlas – mouse brain atlases of the distribution of tetracycline responsive promotors (Boy et al ***Neuroimage*** 2006; Odeh et al ***Neuroimage*** 2011), and Atlas of excitatory amino acid neurotransmitter distributions (Holmseth et al ***Neuroscience*** 2009).

Our accomplishments in terms of organizing and presenting data on complete distribution patterns for gene promotors have contributed to determining the suitability of different TET-OFF mouse lines for creating specific temporally controllable disease models.

In 2005, we established the Preclinical PET/CT imaging unit at the Faculty of Medicine, with the first publications from the University of Oslo in the area of small animal PET imaging and with novel use of 3-D atlas system for assigning location to imaging data (Hjørnevik et al ***Front Neuroinform*** 2007). A range of studies have been performed, including identification of slow metabolic adaptations in brain regions involved in modulation of nociceptive signaling and descending inhibition (Hjørnevik et al ***Pain*** 2008).

A new Navigator database application is released during the last year of the CMBN project period, providing a new and more efficient route for sharing of microscopy and imaging data, coupled to a suite of tools for online viewing and analysis (virtual microscopy).

5 SELECTED PUBLICATIONS

I. Bjaalie JG, Leergaard TB, Lillehaug S, Odeh F, Moene IA, Kjøde JO, Darine D (2005) Database and tools for analysis of topographic organization and map transformations in major projection systems of the brain. *Neuroscience* 136:681-696

This article documents the first database on map transformations in a major circuit of the brain. Maps holding representations of different features (such as body parts and sensory surfaces) are altered in a systematic fashion in the circuits connecting different brain parts. Identifying such transformations reveals important aspects of functional organization of brain connections and allows monitoring of changes taking place as the result of external perturbations or genetic manipulation. In a series of articles published ***in J Comp Neurol***, ***J Neurosci***, ***Eur J Neurosci***, and ***Front Neurosci***, we have collected primary data on connections originating from all parts of the cerebral cortex and targeting the cerebellum. Data have been recorded according to a defined standard and the structured database and accompanying tools facilitates sharing and advanced re-analysis of new combinations of data.

II. Boy J, Leergaard TB, Schmidt T, Odeh F, Bichelmeier U, Nuber S, Holzmann C, Wree A, Prusiner SB, Bujard HB, Riess O, Bjaalie JG (2006) Expression mapping of tetracycline-responsive protein promoter: digital atlasing as a basis for generating cell-specific disease-models. *NeuroImage* 33: 449-462

First publication on the brain-wide distribution of regional and cellular level expression of a transgenic Tet-Off gene promotor, relevant in context of generation and analysis of inducible models based on tetracycline responsive promoter mouse lines. In 2006, the application containing high-resolution microscopic images was new in the field of gene promotor distribution mapping. We have later followed up with mapping of more promoter distributions (Odeh et al ***Neuroimage*** 2011) and this work continues through new collaborations.

III. Hjornevik T, Leergaard TB, Darine D, Moldestad O, Dale AM, Willoch F, Bjaalie JG (2007) Three-dimensional atlas system for mouse and rat brain imaging data. *Frontiers in Neuroinformatics*, 1:4 doi: 10.3389/neuro.11.004.2007

This publication is one of the most viewed articles in the Frontiers publication system. The software has been downloaded by a large number of users through a neuroinformatics infrastructure. The 3-D atlas framework and viewing/analysis tool provided is suitable for assignment of anatomical location and efficient evaluation of spatial distribution patterns present in histological and tomographical (MR/PET/CT) images covering the whole rodent.

IV. Zakiewicz IM, van Dongen YC, Leergaard TB, Bjaalie JG (2011) Workflow and atlas system for brain-wide mapping of axonal connectivity in rat. PLoS One 6(8):e22669

In this article, we demonstrate a systematic, experimental mapping of neural circuits at a mesoscopic scale of resolution suitable for comprehensive, brainwide coverage, using injections of axonal tracers. We detail the method and work flow and provide a database and viewing tool for analysis of more than 1400 high resolution section images, providing detailed data on circuit organization. In the era of complete genomes, knowledge of neuroanatomical circuitry remains surprisingly sparse. Such knowledge is critical, however, for both basic and clinical research into brain function.

V. Kjonigsen LJ, Leergaard TB, Witter MP and Bjaalie JG . (2011) Digital atlas of anatomical subdivisions and boundaries of the rat hippocampal region. *Front Neuroinform* 5:2. doi: 10.3389/fninf.2011.00002

The hippocampus is a commonly used system for a range of investigations of brain in health and disease. The Rat Hippocampus application presented in this publication delivers documentation of structures through the use of interactive viewing tools (allowing inspection of high resolution microscopic data) in combination with encyclopedic information on boundary definitions. Ongoing efforts will result in a new 3-D framework and new opportunties for dynamic viewing and analysis of the hippocampal region.

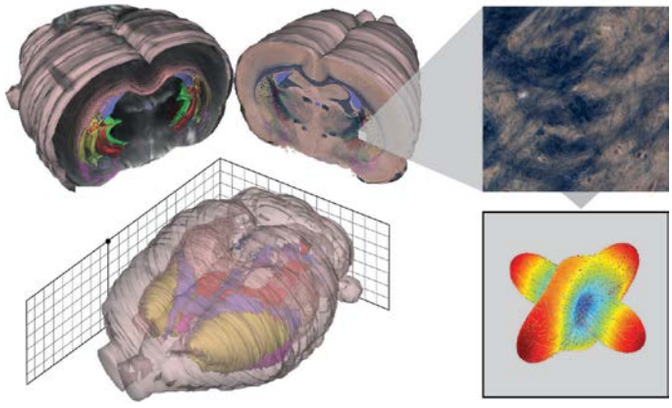

Figure 1. *Localization in the brain. Three-digital rat brain atlas (Hjørnevik et al., 2007, PMID 18974799) serving as spatial template for integrating information about fiber orientations derived from advanced diffusion magnetic resonance imaging measurements and myelin stained histological sections (from White et al., DOI: 10.1002/hbm.21454).*

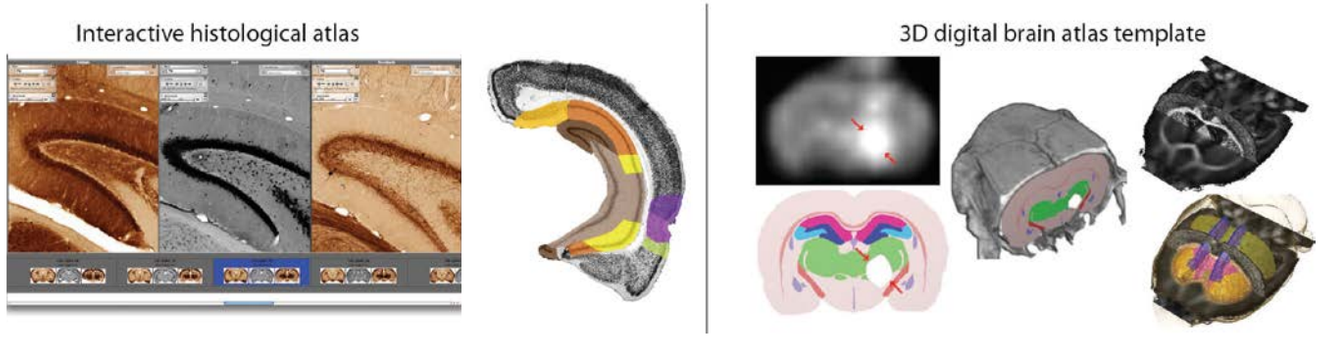

Figure 2. *Digital brain atlasing. (Left) Interactive histological atlas providing detailed anatomical descriptions of boundaries in the rat hippocampus (Kjønigsen et al., 2011, PMID 21519393). (Right) 3D digital rat brain atlas template used to localize tumor associated accumulation of radiolabelled glucose detected by positron emission tomography (from Hjørnevik et al., 2007, PMID 18974799, Veraart et al., 2011, PMID 21749925).*

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Danbolt Group
The Neurotransporter Group

Professor Niels Chr. Danbolt

ABOUT

Our focus is the transporters controlling the actions of neurotransmitter amino acids (GABA and glutamate) and related substances. We are generating quantitative information on transporter protein distributions, numbers and properties, and put this information into 3-dimentional models of brain tissue to perform computer modeling. The group has acquired expertise in the construction of transgenic animals, membrane protein purification and reconstitution in artificial cell membranes, high-resolution imageing, 3D-reconstruction, computer simulations, and antibody production. We are collaborating with a number of foreign and domestic research groups, including groups within CMBN.

RESEARCH FOCUS

The mechanisms controlling neurotransmitter amino acids are hard to study because they are involved in a multitude of different and interconnected processes. Glutamate mediates most of the excitatory (stimulating, activating) signals in the central nervous system, while GABA is a major GABA inhibitory transmitter. This does not only include signals involved in perception, cognition and movements, but also for cell survival, elimination, migration and differentiation, as well as for synapse formation and elimination. To understand what the processes are doing together, it is necessary to do computer simulations, but such simulations require quantitative data on protein properties, distributions and numbers. Further, the tissue ultrastructure must be taken into account: cell volumes and geometry of the extracellular space. In the literature there is little quantitative data that can be used for modeling, and data on distributions are quite confusing, in part due to poorly controlled immunocytochemical studies contradicting each other.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

Our group has been primarily involved in WP3. The topic of this WP was to explore the mechanisms that are responsible for neurotransmitter uptake and detoxification. Work tasks included (A) production of transgenic animals, (B) localization and quantification of the various transporters and their splice variants, (C) regulation and perturbation of transporter function, and (D) modeling of extracellular glutamate. As outlined below, we have addressed all of these topics.

A. Transgenic animals: We have produced five new transgenic mouse lines by floxing the genes encoding EAAT2 (slc1a2) glutamate transporter, three GABA transporters (GAT2, slc6a13; GAT3, slc6a11; BGT1, slc6a12) and glutamine synthetase (GLUL). This represented new technology for our group, and poor infrastructure in the Oslo-area with respect to animal facilities caused unexpected delays and excessive costs. The first data on BGT1 and GAT2 have been published, while data on EAAT2, GAT3 and GLUL will follow.

B. Localization and quantification of the various transporters and their splice variants:

 # Nerve terminal EAAT2: Extracellular glutamate is kept below toxic levels largely by the action of the EAAT2 glutamate transporter, which had only been detected in astrocytes despite well known uptake activity in glutamatergic nerve endings. The physiological importance of the latter uptake had not been determined and the transporter catalyzing it was unidentified (see section 4.2 in *Prog Neurobiol 65, 1*). We realized that this was EAAT2, but because we did cope with the complexity of this project (many samples, several laboratories and many people involved), we got scooped several times. Eventually we got on top of things and completed the project (***Neuroscience*** *157, 80*). We showed that the uptake activity per nerve terminal is higher than expected based on the amount of EAAT2

protein. The results brought up the question of the expression levels of the various EAAT2 splice variants (***Neuroscience*** *162, 1055*) and led us to study functional properties of the EAAT2 protein in order to determine if the high rate of uptake into terminals relative to the amount of transporter protein is due to heteroexchange rather than net uptake. We show, in a refined model of the transporter function, that this is not the case (***manuscript in preparation***). Further, to sort out what the functional role of nerve terminal EAAT2 is, we are using conditional EAAT2 knockout mice (where EAAT2 is selectively deleted in adult astrocytes or in neurons) in collaboration with others. We confirm the above conclusions and add surprising new data (***manuscript in preparation***).

 # EAAT3: Another major study was the determination of the localization and expression levels of the EAAC1 (EAAT3; slc1a1) glutamate transporter subtype. The roles, distribution and expression levels of this transporter have been vividly debated. We have now brought most of these issues to rest (***J Neurosci*** *32, 6000*), but before we could do that, we were forced to resolve a number of issues related to specificity controls (***Neuroscience*** *136, 649*; ***Anat Embryol*** *211, 257*; ***J Histochem Cytochem*** *60, 174*). Further, in connection with a studies of human brain samples, we performed controls in mice and realized that post-mortem proteolysis can be fairly rapid, and, more importantly, the rates of proteolysis may differ both between cells and transporter subtypes as well as between different epitopes within the same protein molecules. As human samples are seldom obtained fresh, the reported differences in transporter expression pattern between rodents and Man may thereby be an artifact (***J Histochem Cytochem*** *60, 811*).

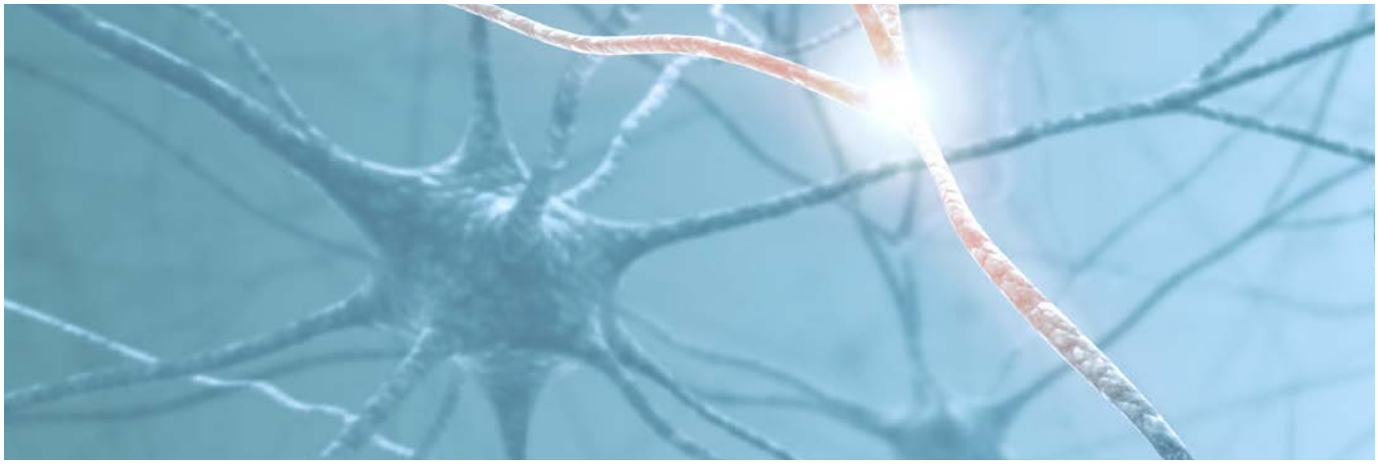
 # The Betaine-GABA transporter (BGT1): The BGT1 gene was deleted to test if the target of EF1502 (an experimental anticonvulsive drug) was indeed BGT1. However, BGT1-deficient mice development normally and had normal seizure susceptibility in a variety of seizure threshold models (corneal kindling, the minimal clonic and minimal tonic extension seizure threshold tests, the 6 Hz seizure threshold test, and the i.v. pentylenetetrazol threshold test). This implies that the reported effects of EF1502 are either artifacts or due to actions on a novel target (***Epilepsy Res*** *95, 70*). In fact, the brain expression levels of BGT1 are too low to support a role in controlling transmitter GABA (***Am J Physiol - Renal Physiol*** *302, F316*). This represents an important correction of the literature.

 # The GABA transporter 2 (GAT2): We also knocked out this transporter, and discovered that it is an important taurine efflux-transporter at the blood brain barrier and also important for hepatocyte taurine uptake (**J Biol Chem**, 287, 35733). Thus, it is not important for inactivation of GABA in brain, but may take part in the regulation of brain water balance. This is also being followed up.

 # Other transporters: We contributed to the identification of a low-affinity excitatory amino acid uptake in hippocampal astrocytes (***Glia*** *56, 990*) and to the determination of the distribution of a glutamine transporter (***Eur J Neurosci*** *15, 1615*). As a side issue, we made antibodies to a glutamate transporter from insects (*Trichoplusia ni*) and found it to be localized in glia (***J Exp Biol*** *205, 2605*).

 # Keeping track: As mentioned above, these projects were complex and it was hard to keep track of data. A collaboration with a start-up company (Science Linker AS) was started to get access to novel database technology. A major advantage with the system from this company is that detailed specifications do not have to be developed in advance as the system is designed for change.

(C) Regulation and perturbation of transporter function: In collaboration with others (Tore Eid, Yale University, USA) we have looked at changes in the distribution of GABA transporters (GAT1 and GAT3) (***Acta Neuropathologica*** *111, 351*)



and in glial glutamate transporters (***Neurobiol Dis*** *25, 319*) in human epileptogenic hippocampus. We have, however, not found clear cut indications that they are clinically important for epilepsy. Eid discovered that loss of glutamine synthetase is a possible mechanism for raised extracellular glutamate in mesial temporal lobe epilepsy (***Lancet*** *363, 28*). We follow up by generating conditional glutamine synthetase knockout mice (unpublished).

EAAT2-mediated glutamate transport can be enhanced by a direct action of a neuroprotective compound (Parawixin1) from *Parawixia bistriata* spider venom on reconstituted glutamate transporter proteins (***Mol Pharmacol*** *72, 1228*). In another collaborative study we found that lipopoly-saccharides upregulate glial glutamate transporters in cultured astrocytes (***Neurochem Res*** *27, 5*; ***Neurochem Int*** *48, 604*).

D. Modeling of extracellular glutamate: We are creating 3D-models of brain tissue based on electron microscopic images. As a side issue, we reconstructed a blood vessel (***Glia*** *58, 1094*). The perisynaptic organization of astroglia is asymmetric and in collaboration with others we show by computer modeling, that this has an impact on transmitter diffusion and removal (***TINS*** *25, 492*; ***Biophys J*** *83, 125*; ***J Neurosci*** *25, 4930*; ***J Neurosci*** *25, 8482*). This is being followed up by more advanced 3D-models of brain tissue as well as more sophisticated mathematics (collaboration with Centre of Mathematics for Applications).

5 SELECTED PUBLICATIONS

I. Furness DN, Dehnes Y, Akhtar AQ, Rossi DJ, Hamann M, Grutle NJ, Gundersen V, Holmseth S, Lehre KP, Ullensvang K, Wojewodzic M, Zhou Y, Attwell D, Danbolt NC (2008) A quantitative assessment of glutamate uptake into hippocampal synaptic terminals and astrocytes: new insights into a neuronal role for excitatory amino acid transporter 2 (EAAT2). Neuroscience 157:80-94.

Here we found that about 80 % of EAAT2 is in astrocytes and about 6 % in the plasma membranes of glutamatergic nerve terminals (adult rat hippocampus, CA1). We also identified electron microscopically the sites of D-aspartate accumulation in hippocampal slices and found that about 3/4 of all terminals in the stratum radiatum CA1 accumulated by means of EAAT2. These terminals were responsible for more than half of all D-aspartate uptake of external substrate in the slices. This was unexpected considering the low amounts of EAAT2 in terminals. There was no glutamate uptake in terminals from conventional EAAT2 knockout mice. Presence of EAAT2 in terminals explains why there are high levels of EAAT2 mRNA in CA3 pyramidal cell bodies, but not why EAAT2 in terminals account for more than half of the uptake of exogenous substrate by hippocampal slice preparations. These finding are now being followed up using conditional EAAT2 mice and by performing computer simulations of transporter function (collaboration with P. Larsson, Miami, USA).

II. Holmseth S, Dehnes Y, Huang YH, Follin-Arbelet VV, Grutle NJ, Mylonakou MN, Plachez C, Zhou Y, Furness DN, Bergles DE, Lehre KP, Danbolt NC (2012) The Density of EAAC1 (EAAT3) Glutamate Transporters Expressed by Neurons in the Mammalian CNS. J Neurosci 32:6000-6013.

The contribution of the EAAT3 glutamate transporter subtype in the clearance of synaptic glutamate has remained controversial, because the density of this transporter in different tissues has not been determined. Here, we determined the concentration of EAAT3 to be 100 times lower than that of EAAT2. Unlike EAAT2 expression, which increases in parallel with circuit formation, only minor changes in the concentration of EAAT3 were observed from E18 to adulthood. In hippocampal slices, photolysis of MNI-D-aspartate (4-methoxy-7-nitroindolinyl-D-aspartate) failed to elicit EAAT3-mediated transporter currents in CA1 pyramidal neurons, and D-aspartate uptake was not detected electron microscopically in spines. Using EAAT3 knock-out mice as negative controls to establish antibody specificity, we show

that these relatively small amounts of EAAT3 protein are widely distributed in somata and dendrites of all hippocampal neurons, but that EAAT3 is not present in glial cells and not in GABAergic terminals.

III. Zhou Y, Holmseth S, Hua R, Lehre AC, Olofsson AM, Poblete-Naredo I, Kempson SA, Danbolt NC (2012) The betaine-GABA transporter (BGT1, slc6a12) is predominantly expressed in the liver and at lower levels in the kidneys and at the brain surface. Am J Physiol Renal Physiol 302:F316-328.

This paper is a follow up on our initial report (***Epilepsy Res*** *95, 70*) showing that deletion of BGT1 has no impact on seizure thresholds. We quantified mRNA levels using TaqMan real-time PCR, produced a number of BGT1 antibodies, and used these to study BGT1 distribution in mice. BGT1 (protein and mRNA) is predominantly expressed in hepatocyte plasma membranes. BGT1 is also present in the kidneys (in particular in basolateral membranes of collecting ducts at the papilla tip) and in the leptomeninges, but brain parenchyma, brain blood vessels, ependymal cells, the renal cortex, and the intestine are virtually BGT1 deficient in 1-3 month old mice. This explains why BGT1 does not appear to play a role in seizure control and why the experimental anticonvulsive drug (EF-1502) works equally well in BGT1-knockout mice. Further, BGT1-deficient mice appeared to tolerate the salt treatment as well as wild-type mice. It is likely that BGT1 plays a role in the metabolism of sulfur amino acids and in protection of the liver against compounds such as ethanol. This is being followed up in collaboration with others.

IV. Zhou Y, Holmseth S, Guo C, Hassel B, Höfner G, Huitfeldt HS, Wanner KT, Danbolt NC (2012) Deletion of the GABA transporter 2 (GAT2, SLC6A13) gene in mice leads to changes in liver and brain taurine contents. J Biol Chem. 287:35733-35746.

In this study we created a new mouse line lacking GAT2 in order to determine the physiological roles of this GABA transporter. The main finding is that deletion of GAT2 reduced liver taurine levels by 50%, without affecting the expression of taurine transporter (TAUT) suggesting an important role for GAT2 in taurine uptake from portal blood into liver. GAT2 was not detected in brain parenchyma proper, excluding a role in GABA inactivation, but it was expressed in the leptomeninges and in a subpopulation of brain blood vessels. Deletion of GAT2 increased brain taurine levels by 20%, suggesting a taurine-exporting role for GAT2 in the brain. These findings are being followed up.

Thus, from our studies it is clear that it is GAT1 and GAT3 that control neurotransmitter GABA in the central nervous system. These transporters are hardly expressed peripherally. In contrast, GAT2 and BGT1 are the only GABA transporters in the liver and kidney. And their main roles here may not be GABA transport. Our data thereby provide important new information on these transporters.

V. Mathiisen TM, Lehre KP, Danbolt NC, Ottersen OP (2010) The perivascular astroglial sheath provides a complete covering of the brain microvessels: an electron microscopic 3D reconstruction. Glia 58:1094-1103.

Here we present a 3D-reconstruction of 14 ffim of a small blood vessel based on electron micrographs from 360 consecutive ulthrathin sections from CA1 (stratum moleculare) of rat hippocampus. The most important finding is that the perivascular endfeet interdigitate and overlap, leaving no slits between them. Only in a few sites do processes—tentatively classified as processes of microglia—extend through the perivascular glial sheath to establish direct contact with the endothelial basal lamina. In contrast to the endfoot covering of the endothelial tube, the endfoot covering of the pericyte is incomplete, allowing neuropil elements to touch the basal lamina that enwraps this type of cell. The 3D reconstruction also revealed large bundles of mitochondria in the endfoot processes that came in close apposition to the perivascular endfoot membrane.

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Klungland Group Genome and Epigenome Maintenance

Professor Arne Klungland

ABOUT

Our research group focuses on; (i) recognition and description of novel enzymes relevant for maintaining or reversing genome and epigenome base modifications and, (ii) addressing the role of such enzymes, and their relevant base modifications, in disease. Most of our studies involve gen-modified animal models and human disease samples. With this approach it is essential to collaborate with numerous research groups, including many within CMBN.

RESEARCH FOCUS

Studying the code of chemical modifications in DNA and RNA is important for understanding fundamental biological processes in health and disease. We aim to understand the role of base modifications in DNA and RNA, including the tightly regulation of their reversal.

One of our major projects relate to the "6th" base in DNA, 5-hydroxymethylcytosine (5-hmC). 5-hmC is generated by the TET enzymes that hydroxylate 5-methylcytosine (5-mC). Our preliminary data support roles of 5-hmC in transcription regulation in addition to its apparent roles in epigenetic reprogramming and as an intermediate in the conversion of 5-methylcytosine (5-mC) to cytosine (C). The 5-hmC modification was recently shown to be absent in cancerous cells. This finding leads to the interesting hypothesis that the 5-hmC modification is essential for normal cellular processes and the loss of this modification may be a hallmark for tumorigenesis. Currently, we are analyzing 4 enzymes identified through their specific interactions or activities with 5-hmC containing DNA.

DNA has been the main focus for studying genome and epigenome base modifications. However, functional RNAs and reversible RNA modifications have entirely changed our and the scientific communitiy's view on RNA. The fat mass and obesity-associated dioxygenase FTO/ALKBH9 reverses 6-methyladenine (6-mA) modifications in RNA. The role of 6-mA in mRNA is currently unknown. We have identified other enzymes that efficiently reverse the 6-mA modifications in mRNA and we are currently analyzing the role of 6-mA in meiosis and relevant human diseases.

We are continuing our research on DNA repair processes, with particular emphasis on the repair of methylation products in DNA, in addition to inflammation induced etheno-adducts. While the repair of oxidative lesions has been the focuses of numerous research groups, including ours, it appears that methylation products must be particularly important as 3 fundamentally different repair processes have evolved to handle such lesions. Our focus is on the repair carried out by oxidative demethylation; a process with remarkable similarities to the hydroxylation of 5-mC to 5-hmC and the demethylation of 6-mA in mRNA.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

In this report, we will focus on four major themes from the CMBN initiative in 2002.

First, concerning the topic "DNA stability and neurodegeneration". From our application, "*The Centre shall take on a leading role in elucidating the role of DNA repair and genome maintenance mechanisms in preventing neurological disease and cancer brain ageing*". Some central publications include the recognition of OGG1 as a modifier of Huntingtons Disease (Kovtun et al ***Nature*** 2007 and fig. 1). Here we show that the age-dependent somatic mutation associated with Huntington's disease occurs in the process of removing oxidized base lesions, and is remarkably dependent on a single base excision repair enzyme, 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1). Furthermore, we have identified two form of CAG expansion in Huntington's disease mice; continuous and periodic expansion of CAG repeats in (Møllersen et al ***PLoS Genet*** 2010). These studies

were highly dependent upon collaboration with the Bjørås and Rognes group. We have also, in close collaboration with Linda Bergersen and Johan Storm, characterized a rather surprising consequence of apyrimidinic sites in the mitochondrial genome of forebrain neurons in mice (Lauritzen et al ***Mol Cell Biol*** 2010; Lauritzen et al ***DNA repair*** 2011).

For the second CMBN objective "*DNA repair, cancer and ageing*" which is described by Visions 1 and 2 in WP-2 "*Ageing, DNA repair and brain function*" our most surprising publication describes the identification of three enzymes, Alkbh2, Alkbh3 and Aag, jointly being absolutely required for the protection against innflamation. Chronic inflammation is strongly associated with an increased risk of cancer, and more than 15% of cancer deaths worldwide are associated with an underlying infection or inflammatory condition (Study directed by Leona Samson; Calvo et al ***J Clinical Invest*** 2012 and fig. 2). Also, we have described a possible role for oxidative stress in transcriptional mutagenesis (Study directed by Paul Doetsch, Saxowsky et al ***Proc Natl Acad Sci USA*** 2008) and further characterized the role of a structure specific endonuclease (Larsen et al ***Mol Cell Biol*** 2003; Larsen et al ***Canc Res*** 2008). Additionally, we have characterized the repair and mutagenesis at oxidized DNA base lesions in the developing brain in relation to OGG1 expression (Larsen et al Oncogene 2006).

Third, we have also identified novel genes and mechanisms for maintaining DNA modifications (WP-1: "*....elucidation of novel repair genes and mechanisms*"). Studies include cloning and preliminary characterization of Endonuclase V from mouse (Moe et al ***Nucl Acids Res*** 2003), further characterization of Alkbh2 and Alkbh3 (which paved the basis of the ***J Clinical Invest*** study mentioned above; Ringvoll et al ***EMBO J*** 2007; Ringvoll et al ***Canc Res*** 2008). Surprisingly, we also found that the repair of certain methylated bases in DNA (1-methyladenine and 3-methylcytosine) is excised by a DNA glycosylase in Archea (Leiros et al ***EMBO J*** 2007; Archea has no AlkB homologs). We have also identified the relevant *in vivo* substrates for Alkbh4 and Alkbh5 (in review and Zheng et al ***Mol Cell*** 2013).

Fourth, we have been fortunate to collaborate, and provided support in relation to methods in molecular biology, to quite a few neuroscience focused project which is described in WP-3, "*Dynamics of transport – potential for therapy targeted to glutamate systems*" (Vision 2). Papers include Haj-Yasein et al ***Glia*** 2011; Haj-Yasein et al ***Proc Natl Acad Sci USA*** 2011; Thrane et al ***Proc Natl Acad Sci USA*** 2011; Strømme et al ***Brain*** 2011.

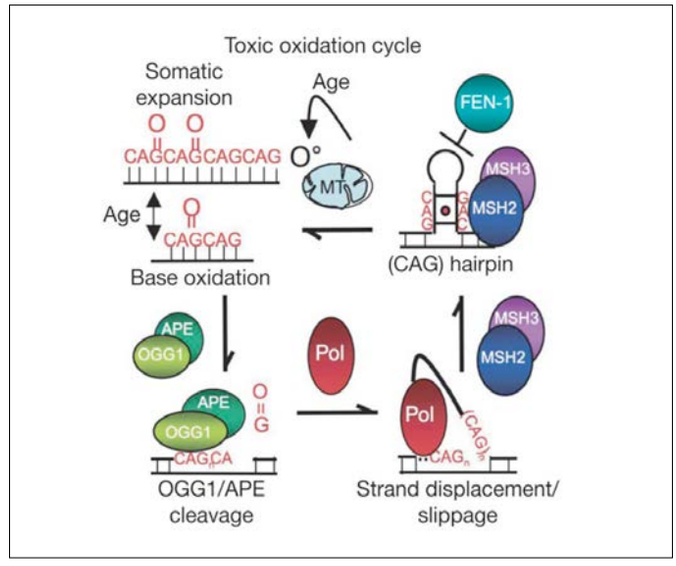

Fig. 1 'Toxic oxidation cycle' model for age-dependent somatic CAG expansion. *Endogenous oxidative radicals (O°) arising from mitochondrial (MT) respiration creates oxidative DNA lesions. Under conditions of normal BER, OGG1/APE cleavage produces a nick, and polymerase (Pol) facilitates hairpin formation during gap-filling synthesis. CAG hairpins are stabilized by MSH2/MSH3 binding (red dot is a mismatch in the stem) and escape FEN-1 loading and cleavage owing to a hidden 5′ end. The hairpin intermediate is processed to restore duplex DNA generating a longer CAG template, which is again subject to oxidative DNA damage. The cycle continues with age. See Kovtun et al Nature 2007 for details.*

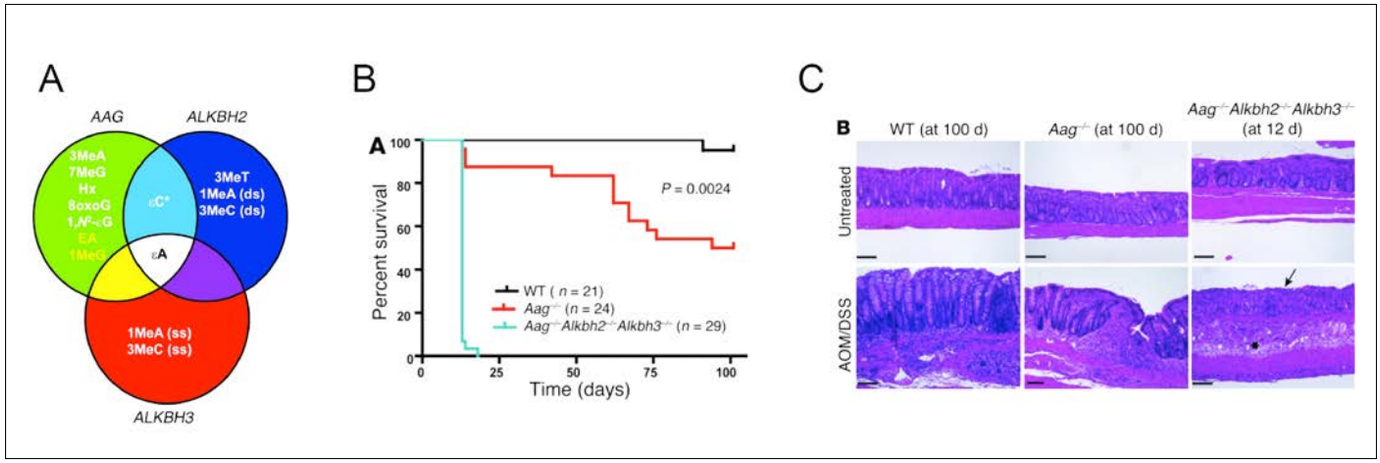

Fig. 2 Aag$^{-/-}$Alkbh2$^{-/-}$Alkbh3$^{-/-}$ mice do not survive AOM+DSS treatment. (A) *Published nucleic acid substrates for the AAG, ALKBH2 and ALKBH3 enzymes. Substrates for the AAG, ALKBH2, and ALKBH3 enzymes have been illustrated either in vitro or in vivo including 3-methyladenine (3MeA), 7-methylguanine (7MeG), hypoxanthine (Hx), 8-dihydro-8-oxoguanine (8oxoG), 7N6-ethanoadenine (EA), 1,N2-ethenoguanine (eG), 1-methylguanine (1MeG), 3,N4-ethenocytosine (eC), N6-ethenoadenine (eA), 3-methylthymine (3MeT), 1-methyladenine (1MeA), and 3-methylcytosine (3MeC).* indicates that AAG binds but is unable to excise eC base lesions. Lesions listed in yellow are known substrates of bacterial AlkB; ALKBH2 or ALKBH3 have yet to be tested for the ability to excise these lesions.* **(B)** *Kaplan-Meier survival curves illustrate complete lethality of Aag-/-Alkbh2-/-Alkbh3-/- mice following the first DSS cycle.* **(C)** *H&E pictures illustrate colon pathology from Aag-/-Alkbh2-/-Alkbh3-/- mice harvested two day following DSS withdrawal. H&E pictures from WT and Aag-/- mice illustrating colon pathology at the completion of the AOM+DSS treatment. Consistent with the completion of the AOM+DSS treatment in the WT and Aag-/- cohorts, their colons exhibited regions of hyperplasia, inflammation and minimal dysplasia. *indicates submcusoal edema and associated scattered inflammatory cells, arrow indicated epithelial erosion and necrosis. (From Calvo et al J Clin Invest 2012)*

5 SELECTED PUBLICATIONS

I. Larsen E, Gran C, Sæther BE, Seeberg E, Klungland A. Proliferation failure and gamma radiation sensitivity of Fen1 null mutant mice at the blastocyst stage. *Mol Cell Biol* 2003 23:5346-53.

This is my first last-author paper. The continued work on FEN1 is due to an interest in elucidating the role of this highly structure specific endonuclease in genome (in) stability. This interest commenced during a fruitful post doc study with Tomas Lindahl at Clare Hall laboratories and the initial characterization of FEN1 in base excision repair (BER; Klungland and Lindahl ***EMBO J*** 1997). In the first study (paper I) we show that FEN1, as expected, is absolute required for viability due to its function in DNA repair, as well as in DNA replication. In more recent studies we have further elucidated the role of FEN1 in proliferation and repair and established a defined murine model for analyzing the kinetics of the endogenously expressed Fen1 protein (Larsen *et al* ***Canc Res*** 2008, Kleppa *et al* ***Nucl Acids Res*** 2012)

II. Ringvoll J, Nordstrand LM, Vågbø CB, Talstad V, Reite K, Aas PA, Lauritzen KH, Liabakk NB, Bjørk A, Doughty RW, Falnes PØ, Krokan HE, Klungland A. Repair deficient mice reveal mABH2 as the primary oxidative demethylase for repairing 1meA and 3meC lesions in DNA. *EMBO J* 2006 25:2189-98

The studies of the nine AlkB homologs (ALKBH1-9) have been the major focus of our group since 2004. The first paper we published on the AlkB homologs (paper II) revealed an essential role of Alkbh2 for removing spontaneously arising methylation adducts in the mouse genome. Somewhat unexpected, we found that Alkbh3 have no additive effect on the accumulation of DNA damage in Alkbh2 deficient mice. In more recent studies we have further characterized the enzymatic repair of methyl lesions in DNA (Leiros *et al* ***EMBO J*** 2007) and also identified some vital function of the AlkB homologs in the protection agains cancer (Calvo *et al* ***J Clin Invest*** 2012, Songe-Møller *et al* ***Mol Cell Biol*** 2010, van

den Born *et al* ***Nat Comm*** 2011, Ringvoll *et al* ***Canc Res*** 2008). Quite a few manuscripts, including the first description of the substrates for Alkbh4 and Alkbh5, are currently under review. Hans Krokan (NTNU), Pål Falnes (UiO and CMBN), Yungui Yang (Beijing) and Chuan He (Chicago) have been, and still are, invaluable partners for the characterization of the AlkB homologs. One of our current projects investigates the possible redundancy provided by overlapping activities of the obesity associated AlkB homolog (FTO/Alkbh9) and Alkbh5 (in progress).

III. Kovtun IV, Liu Y, Bjoras M, Klungland A, Wilson SH, McMurray CT. OGG1 initiates age-dependent CAG trinucleotide expansion in somatic cells. ***Nature*** **2007 447:447-52**

The role of DNA repair in neurodegenerative disease was one of the fundamental subjects to be addressed with the 2002 CMBN initiative. In collaboration with Cynthia McMurray we (Bjørås and Klungland) show that the DNA glycosylase OGG1 and the repair of oxidized base modifications in DNA are key factors initiating CAG expansions in the expanded Huntington disease (HD) triplet. In a new study (also together with Bjørås) the role of another DNA glycosylase, Neil1, in CAG stability is elucidated and further corroborate on the role of oxidative base damage in neurodegenerative disease (Møllersen et al ***Hum Mol Genet*** 2012).

IV. Møllersen L, Rowe AD, Larsen E, Rognes T, Klungland A. Continuous and periodic expansion of CAG repeats in Huntington's disease R6/1 mice. ***PLoS Genet*** **2010 6:e1001242**

Somatic CAG expansion in HD varies between organs, and greater instability correlates with neuropathology. Yet, the fundamental mechanisms of somatic CAG repeat instability are poorly understood. In collaboration with the group of Torbjørn Rognes we demonstrate continuous small CAG expansions in most somatic tissues, and a dramatic, and apparently irreversible, periodic expansion in striatum and cortex. Expansion profiles displaying this kind of periodicity of the expansion profiles have not previously been reported and imply that mechanistically distinct expansion processes occur in different tissues.

V. Robertson AB, Dahl JA, Vågbø CB, Tripathi P, Krokan HE, Klungland A. A novel method for the efficient and selective identification of 5-hydroxymethylcytosine in genomic DNA. ***Nucleic Acids Res*** **2011 39:e55**

Based on the remarkable similarities in the enzymology of the TET and AlkB enzymes, we have also initiated several studies on the biological roles of 5-hmC. Some of these studies are based on our first 5-hmC publication which enables us to identify genomic regions containing 5-hmC. This method is licensed and several product relating to this patent are released by ZYMO research (see also Robertson et al ***Nat Prot*** 2012).

Our present studies focus on the characterization of several proteins that specifically interact or process DNA regions containing 5-hmC modifications (unpublished). It is also worth mentioning that the 5-hmC base modification is particularly frequent in specific brain regions and some of our projects (in progress) elaborate on the plasticity of the 5-hmC modification in rat brains stimulated by various environmental impact.

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Koomey Group
Molecular and Cellular Basis of Microbial Pathogenesis

Professor Michael Koomey

ABOUT

Our research is centered on studies of how bacterial pathogens cause disease in man. In particular, we focus primarily on bacterial surface organelles termed Type IV pili (Tfp) or fimbriae as Tfp expressing bacterial pathogens are responsible for an extensive amount of morbidity and mortality worldwide. We use molecular biology strategies, together with classical genetic, genomic and proteomic approaches to elucidate the mechanisms of Tfp biogenesis and the structure/function relationships accounting for Tfp - associated phenotypes. The intention is that by understanding the molecular basis for these processes, it will be possible to design rational approaches to preventing and controlling disease.

RESEARCH FOCUS

Despite significant advances, there remain surprisingly large numbers of bacterial diseases for which no vaccines are available. Moreover, resistance to standard antibiotic regimens is evolving at a dramatic rate. It is thus crucial that we gain more basic knowledge relating to the mechanisms by which bacterial pathogens cause disease and interact with the human host at both the cellular and molecular levels. One key point of intervention involves blocking steps relevant to colonization of human tissue, the initiating event in disease. Type IV pili (Tfp) are extracellular proteinaceous filaments that serve as critical colonization factors in a vast number of bacterial pathogens responsible for an extensive amount of morbidity and mortality worldwide. Tfp expression is also associated with horizontal gene transfer and therefore contributes to the evolution of pathogenic and antibiotic resistant microbes. Moreover, retraction of single Tfp filaments (required for Tfp - mediated motility) generates forces in excess of 100 pN making them the most powerful biological molecular motor yet characterized. As such, Tfp play central roles in prokaryotic cell biology and disease pathogenesis. Based on both its relevance to other human diseases and its amenability to *in vitro* manipulation and analysis, we have chosen the human pathogen *Neisseria gonorrhoeae*, the agent of gonorrhea, as a principle model system. We have aimed to understand and to elucidate the mechanisms of Tfp biogenesis and the structure/function relationships accounting for Tfp associated phenotypes. To date, our studies have established a number of genotype - phenotype relationships underlying gonococcal Tfp biology. Moreover, we have extended these studies to examine Tfp - related processes in *N. meningitidis* (the aetiologic agent of epidemic meningitis), *Pseudomonas aeruginosa* (the major cause of opportunistic infections in humans), and *Vibrio cholerae* (the agent of cholera) and have documented a highly conserved set of structure – function relationships.

We are also continuing studies that evolved from the Tfp studies. These include the identification and characterization of unique post-translational modifications (PTM) (O-linked protein glycosylation and direct covalent protein modifications with phosphoethanolamine and phosphocholine). Subsequently to our neisserial work, highly related systems have been identified in a number of important bacterial pathogens by us and others. Future efforts are focused on the structural and functional significance of these PTMs. Finally, we are using species within the genus *Neisseria* to understand the evolution of highly related pathogens and symbionts within the human host.

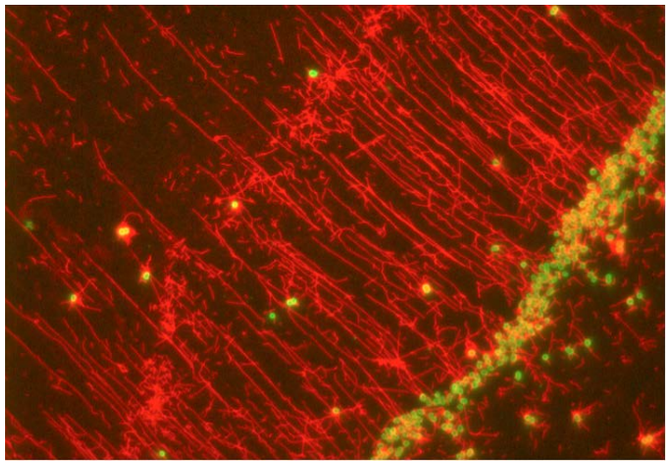
ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

In this report, we will focus on the major theme from the cmbn initiative in 2002 relevant to our work (v4. "*The centre will further develop world-class expertise within microbial pathogenesis related to human disease in general and neurological disease in particular*"). Using species in the genus *Neisseria* (including *N. meningitidis*) as a model system, we have made a number of discoveries relating to how bacteria interact with host cells, alter their surface structure and evolve.

Tfp function and dynamics: Tfp expression is tightly linked to a variety of phenotypes relevant to human infection including adherence, motility and DNA uptake during natural transformation. Tfp are also dynamic filamentous polymers, they undergo rounds of extension and retraction modelled as pilin subunit polymerization and depolymerization events. Tfp retraction is critical to non-flagellar based motility and influences interactions with human host cells. Together with Xavier Nassif´s group, we showed for the first time that meningococcal Tfp retraction is controlled by expression of the pilus-associated PilC adhesin protein (Moran et al, ***EMBO J***, 2004). We went on to identify a number of other proteins and factors influencing neisserial Tfp function and dynamics (Maier et al, ***PNAS***, 2004; Winther-Larsen et al, ***Mol Microbiol***, 2005; Aas et al ***Mol Microbiol*** 2007; Winther-Larsen et al, ***J Bacteriol*** 2007, Clausen et al, ***Biophys J*** 2009; Holz et al, ***Phys Rev Lett***, 2010). We also showed that similar relationships are operating in *Pseudomonas aeruginosa*, an important human opportunistic pathogen (Heiniger et al, ***Cell Microbiol***, 2010).

Unique PTMs in bacteria: Together with Anne Dell, we discovered two unique post-translational modifications (PTM) utilizing the zwitterionic phospho-forms phosphoethanolamine and phosphocholine on the pilus subunit protein (Hegge et al, ***PNAS*** 2004). Subsequently, we published papers related to the multisite and hierarchical nature of these PTMs, the identification and characterization of the enzyme mediating the PTM process (PptA), and PTM targetting of other proteins (Aas et al, ***JBC***, 2006; Næssen et al, ***J Bacteriol*** 2008; Anonsen et al, ***Infect Immun***, 2012). Interestingly PptA and these modifications are retsricted to pathogenic neisserial species and a recent study in the human pathogen *Campylobacter jejuni* reported an identical PTM and associated machinery that impacts on virulence. Since 2004, we have extensively studied neisserial O-linked protein glycosylation and have published a number of dominant papers relating to glycan biosynthesis, structure and antigenicity, protein substrate targetting and glycosylation and the repertoire of glycoproteins in *N. meningitidis*, *N. gonorrhoeae* and non- pathogenic species (Aas et al, ***Mol Microbiol***, 2007; Vik et al, ***PNAS***, 2009; Bøvrud et al, ***J Bacteriol***, 2010; Bøvrud et al, ***PNAS***, 2011; Hartley et al, ***Biochemistry***, 2011). The work of Vik et al was the first identification of a broad-spectrum, O-linked protein glycosylation system in Bacteria. More recently we have expanded studies of protein glycosylation into the important human pathogens *Francisella tularensis* (Egge- Jacobsen et al, ***J Bacteriol***, 2011) as well as *Vibrio cholerae* and *Burkholderia* species (Gebhardt et al, ***Glycobiology***, 2012). We have also just shown that protein glycosylation of the Tfp subunit protein can affect Tfp biogenesis and dynamics (Vik et al, ***Mol Microbiol*** 2012).

Bacterial in host evolution: In 2010, we published the discovery that a single structural alteration in protein component of the sole respiratory oxidase (owing to a SNP) was uniquely and completely disseminated within the species *N. meningitidis* (Aspholm et al, ***PLoS Pathogen***, 2010). Moreover, we showed that mutation altered the electron flow circuitry in the respiratory chain. These findings provided an unprecedented example of how rare changes in core metabolic proteins can be connected to significant macroevolutionary shifts. They also showed how evolutionary change at the molecular level can be linked to metabolic innovation and its reversal as well as demonstrating how genotype can be used to infer alterations of the fitness landscape within a single host.



Tfp elaborated by ***Neisseria gonorrhoeae*** *expressing the PilA pilin subunit protein of* ***Pseudomonas aeruginosa*** *(immunofluorescence microscopy showing the Tfp [red] and diplococcal cells [green]) From Winther-Larsen et al* ***J Bacteriol*** *2007.*

5 SELECTED PUBLICATIONS

I. Hegge FT, Hitchen PG, Aas FE, Kristiansen H, Lovold C, Egge-Jacobsen, W, Panico, M, Leong, WY, Bull, V, Virji, M, Morris HM, Dell A, Koomey M. Unique modifications with phosphocholine and phosphoethanolamine define alternate antigenic forms of *Neisseria gonorrhoeae* type IV pili. *Proc Natl Acad Sci USA* 2004 101: 10798-10803.

This works reports the serendipitous discovery and characterization of protein modification with phosphoethanolamine and phosphocholine. Such modifications were unprecedented in any biological system. PTMs of these types have now been identified in other bacterial systems. This work led to our intense focus on bacterial PTMs resulting in over 14 papers in the last 8 years on this topic in important pathogens within *Neisseria*, *Francisella*, *Burkholderia* and *Vibrio* species.

II. Maier, B, Koomey M, and M. P. Sheetz MP. A force-dependent switch reverses type IV pilus retraction. *Proc Natl Acad Sci USA* 2004 101:10961-10966.

Type IV pili are the the strongest molecular motors reported and pilus dynamics are important for virulence, motility, and DNA transfer in a wide variety of prokaryotes. Pilus retraction is controlled by PilT proteins that are homologous with AAA ATPases including chaperones and mechanoenzymes. Like other AAA ATPases, PilT has a hexameric structure, hydrolyzes ATP supports pilus retraction, most likely by depolymerization of the pilus. Using laser tweezer technologies and defined mutant, we found that force can cause extension of pili at low levels of PilT. This placed important constraints on possible mechanisms of pilus retraction. Variation of PilT concentration, symmetry in the force-dependent extension and the retraction processes reinforced the hypothesis that both external force and PilT dictate the direction of pilus dynamics. This work has led to 8 subsequent publications examining the role of PilT in Tfp biology including the recent elucidation of the role of Tfp retraction in the adherence of *Pseudomonas aeruginosa* to primary human tissue (Heniger et al ***Cell Microbiol*** 2010).

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

The co-ordinated extension and retraction of Tfp drives processes that play important roles in many physiological contexts. Moreover, the properties of Tfp are attributed, in part, to proteins other than pilin subunits that associate or interact with the organelle. The identification and characterization of such proteins is therefore important to understanding how Tfp function. In the absence of an *in vitro* system in which these events can be reconstituted, factors contributing to Tfp biology have been identified almost exclusively from genetic and loss-of-function studies. Here, we used reverse genetics to show that a set of five proteins sharing structural similarities to Tfp pilin subunit proteins, dramatically influence Tfp function and dynamics in the human pathogen *N. gonorrhoeae*. These findings have been confirmed in other Tfp expressing pathogens including *Pseudomonas aeruginosa* (Heniner et al ***Cell Microbiol*** 2010).

IV. Vik A, Aas FE, Anonsen JH, Bilsborough S, Schneider A, Egge-Jacobsen W, and Koomey M. Broad spectrum O-linked protein glycosylation in the human pathogen *Neisseria gonorrhoeae*. *Proc Natl Acad Sci USA* 2009 106: 4447-4452.

Here we identified and characterized a general O-linked glycosylation system that targets structurally and functionally diverse groups of membrane-associated proteins in *Neisseria gonorrhoeae*. This was the first such system to be identified in bacteria.

Along with their common trafficking within the periplasmic compartment, the protein substrates shared quasi-related domains bearing signatures of low complexity that were demonstrated to encompass sites of glycan occupancy. Thus, 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. Further studies defining the gonococcal glycoproteome confirm and extend these studies (work in progress).

V. Aspholm M, Aas FE, Harrison OB, Quinn D, Vik A, Viburiene R, Tonjum T, Moir J, Maiden MC, Koomey M. Structural alterations in a component of cytochrome c oxidase and molecular evolution of pathogenic *Neisseria* in humans. PLoS Pathogen 2010 6: e1001055

Three closely related bacterial species within the genus Neisseria are of importance to human disease and health. *Neisseria meningitidis* is a major cause of meningitis, while *Neisseria gonorrhoeae* is the agent of the sexually transmitted disease gonorrhea and *Neisseria lactamica* is a common, harmless commensal of children. Comparative genomics have yet to yield clear insights into which factors dictate the unique host-parasite relationships exhibited by each since, as a group, they display remarkable conservation at the levels of nucleotide sequence, gene content and synteny. Here, we discovered two rare alterations in the gene encoding the CcoP protein component of cytochrome cbb(3) oxidase that are phylogenetically informative. One is a single nucleotide polymorphism resulting in CcoP truncation that acts as a molecular signature for the species *N. meningitidis*. We go on to show that the ancestral *ccoP* gene arose by a unique gene duplication and fusion event and is specifically and completely distributed within species of the genus Neisseria. Surprisingly, we found that strains engineered to express either of the two CcoP forms conditionally differed in their capacity to support nitrite-dependent, microaerobic growth mediated by NirK, a nitrite reductase. Thus, we propose that changes in CcoP domain architecture and ensuing alterations in function are key traits in successive, adaptive radiations within these metapopulations. These findings provide a dramatic example of how rare changes in core metabolic proteins can be connected to significant macroevolutionary shifts. They also show how evolutionary change at the molecular level can be linked to metabolic innovation and its reversal as well as demonstrating how genotype can be used to infer alterations of the fitness landscape within a single host.

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Krauss Group

Professor Stefan Krauss

ABOUT

The main goal of the group is to gain understanding on the signaling pathways Wnt/beta-catenin and Hh/oxysterol in the context of development, stem cells and cancer. Using transgenic models and chemical biology we develop tools to analyze and alter these pathways. A long term goal is to develop novel therapeutics that attenuates Wnt/beta-catenin and Hh/oxysterol signaling.

RESEARCH FOCUS

The dual Wnt/beta-catenin and Hh/oxysterol signaling pathways are one of the oldest signaling systems that date back to the first metazoans and are implied in stem cells, in a broad variety of developing organ systems, and in selected adult niches. Alterations in Wnt/beta-catenin and Hh/oxysterol signaling are central in multiple diseases, including degenerative diseases, neurological diseases, metabolic diseases, and a substantial number of cancers. Specific organ systems that depend on either signaling systems during development and/or in their adult steady state include the cerebral cortex, hippocampus, eye, lens, spinal cord, limbs, bone, cartilage, somites, neural crest, skin, teeth, gut, lungs, heart, pancreas, liver, kidneys, mammary glands, the hematopoetic system and the reproductive system. Hence, studying the pathways is of fundamental importance in biomedical research. Moreover, there is substantial interest in developing for analytical and therapeutic purposes specific tools that can influence and alter components of Wnt/beta-catenin and Hh/oxysterol signaling.

Coming from a developmental biology background, our laboratory has since 1991 worked on specific aspects of Wnt signaling, and identified in 1993 the Shh morphogen. In the last 20 years we have studied the implications of the Wnt/beta-catenin and Hh/oxysterol signaling systems in anterior neural tube development using a variety of model-systems such as amphioxus, zebrafish and mouse.

As we and others realized the extraordinary importance of developmental control genes in biomedical research, we are now using the Hh and Wnt pathways to develop novel therapeutic tools, in particular directed towards Wnt/beta-catenin signaling. The broad implications of Hh/oxysterol and Wnt/beta-catenin signaling in development, the adult body, and in disease, render it a prime target for pharmacological research and development. One of our drugs (OD270), a highly specific tankyrase antagonist, has reached lead status and serves at current as industry benchmark.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

Following the outline of the CMBN proposal, we have developed a genetic tool to manipulate gene expression and in particular Wnt/beta-catenin signaling in the forebrain. This was achieved by the hitherto most specific forebrain enhancer D6 (van den Bout et al., ***Mech Dev*** 2002; Machon et al.,***Neuroscience*** 2003). D6 based transgenic models were subsequently used to study aspects of forebrain development and Wnt/beta-catenin as well as Hh/oxysterol signaling in a number of collaborative studies (Machon et al., ***Neuroscience*** 2003; Petersen et al., ***Nat Neurosci*** 2004; Backman et al., ***Dev Biol*** 2005; Kadowaki et al., **Dev Biol** 2007; Kreslova et al., ***Genesis*** 2007; Machon et al., ***Dev Biol*** 2007; Solberg et al., ***Dev Dyn*** 2008; Faedo et al., ***Cereb Cortex*** 2008). In particular we characterized the implications of Wnt/beta-catenin signaling in fate determination of the dorsal forebrain and in the development and origins of the dentate gyrus. A major finding was the identification of a dynamic gradient of Wnt signaling controls initiation of neurogenesis in the mammalian cortex and cellular specification in the hippocampus . The D6 enhancer was also used to isolate cortex specific neurospheres and to study their fate alteration when grown *in vitro* (Rappa et al., ***Neuroscience*** 2004; Machon et al., ***Mol Cell Neurosci 2005***), and as a marker to differentiate mouse embryonic stem cells into cortical neurons (Jing Y et al., ***Cell Mol Neurobiol*** 2011).

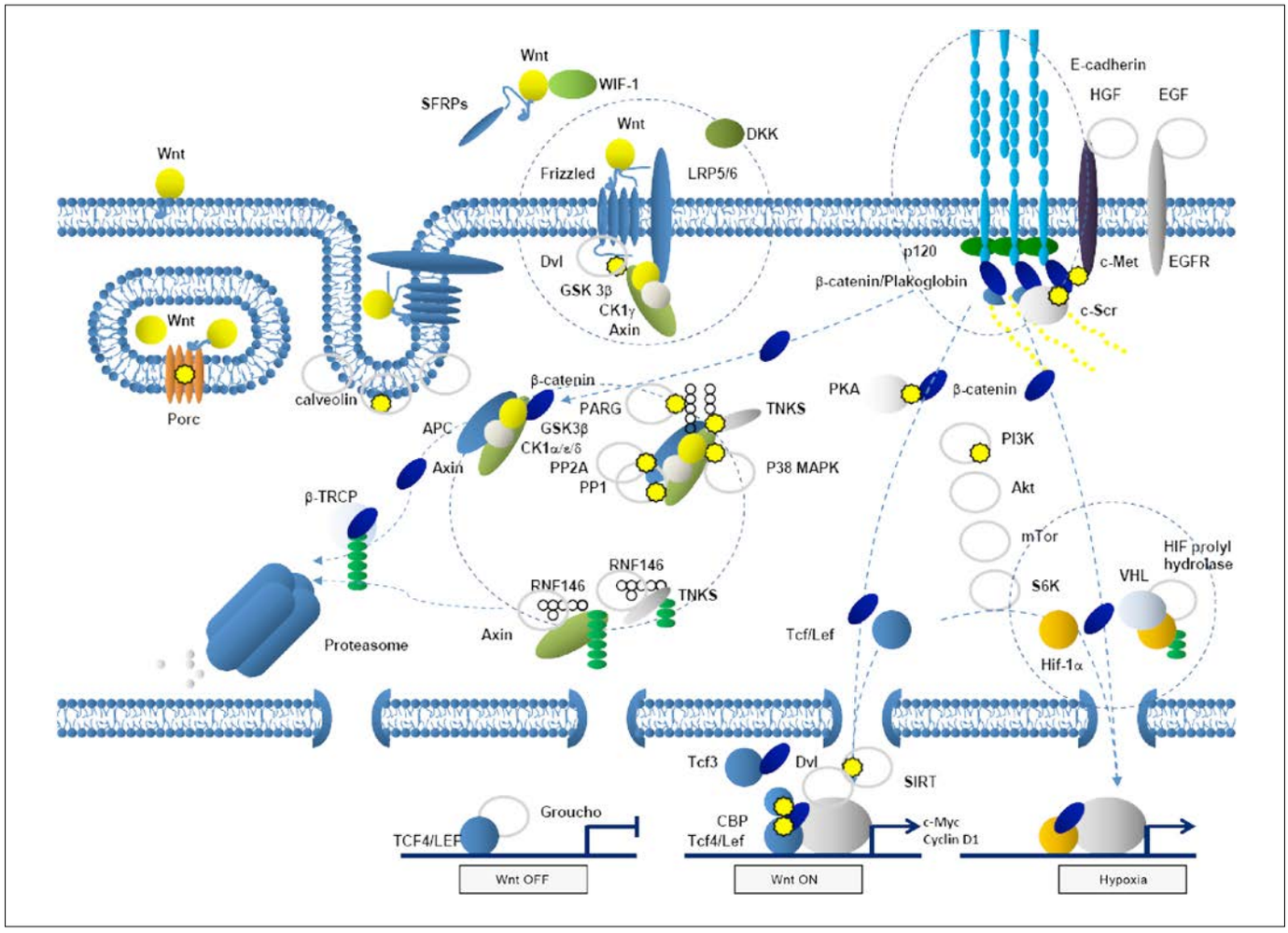

Figure 1. *Simplified schematic representation of drug targets (yellow stars) in Wnt/β-catenin mediated signaling. Four key aspects that regulate β-catenin mediated signaling are highlighted: The destruction complex, the Wnt/β-catenin signalosome, cadherin junctions, and the hypoxia sensing system.*

In a second development we have worked on developing possible therapeutic tools that allow manipulating key elements in the Wnt/beta-catenin and Hh/oxysterol signaling pathways. One strategy was to build up a technology to alter genetic sequences by gene editing. This was initially done by ss oligonucleotides (Olsen et al., ***Gene Ther*** 2005; Olsen et al., ***J Gene*** Med 2005) , and subsequently by zinc finger nucleases (Olsen et al., ***DNA repair*** 2009; Olsen et al., ***BMC Mol Biol*** 2010).

The second strategy was based on a chemical biology platform that allowed us to identify and develop specific Wnt/beta-catenin and Hh/oxysterol inhibitors (Waaler et al., ***Cancer Res*** 2011, Strand et al., ***PLoS One*** 2011; Waaler et al., ***Cancer Res*** 2011). One of the identified and optimized substances is a first of its class tankyrase specific inhibitor OD270 (a JW74 derivative) that serves at current as the industry standard for an *in vivo* viable Wnt/beta-catenin inhibitor. For the OD270 chemical series, three patents were filed and collaboration with a large pharmaceutical company has been initiated. In ongoing studies, the inhibitors are tested in various *in vitro* and *in vivo* models. This collaboration could be of particular interest since there is an unmet need for viable antagonists to Wnt/beta-catenin signaling as potential human therapeutics.

5 SELECTED PUBLICATIONS

I. J Waaler, O Machon, L Tumova, H Dinh, V Korinek, S R Wilson, J E Paulsen, N M Pedersen, T J Eide, O Machonova, D Gradl, A Voronkov, J P von Kries and S Krauss (2012) The novel tankyrase inhibitor JW55 decreases canonical Wnt signaling in colon carcinoma in vitro and reduces tumor growth in conditional APC mutant mice in vivo Cancer Research Cancer Res. 2012 Jun 1;72(11):2822-32. Epub 2012 Mar 22.

Increased nuclear accumulation of beta-catenin, a mediator of canonical Wnt signaling, is found in numerous tumors and is frequently associated with tumor progression and metastasis. Inhibition of Wnt/beta-catenin signaling therefore is an attractive strategy for anticancer drugs. In this study, we have identified a novel small molecule inhibitor of the beta-catenin signaling pathway, JW55, that functions via inhibition of the PARP domain of tankyrase 1 and tankyrase 2 (TNKS1/2), regulators of the beta-catenin destruction complex. Inhibition of TNKS1/2 poly (ADP-ribosyl) ation activity by JW55 led to stabilization of AXIN2, a member of the beta-catenin destruction complex, followed by increased degradation of beta-catenin. In a dose-dependent manner, JW55 inhibited canonical Wnt signaling in colon carcinoma cells that contained mutations in either the APC (adenomatous polyposis coli) locus or in

an allele of beta-catenin. In addition, JW55 reduced XWnt8-induced axis duplication in Xenopus embryos and tamoxifen-induced polyposis formation in conditional APC mutant mice. Together, our findings provide a novel chemotype for targeting canonical Wnt/beta-catenin signaling through inhibiting the PARP domain of TNKS1/2

II. Waaler J, Machon O , von Kries JP, Wilson SR, Lundenes E, Wedlich D, Gradl D, Paulsen JE, Machonova O , Dembinski JL , Dinh H, Krauss S (2011), **Novel synthetic antagonists of canonical Wnt signaling inhibit colorectal cancer cell growth , Cancer Res, 71 (1),** 197-205

Canonical Wnt signaling is deregulated in several types of human cancer where it plays a central role in tumor cell growth and progression. Here we report the identification of two new small molecules that specifically inhibit canonical Wnt pathway at the level of the destruction complex. Specificity was verified in various cellular reporter systems, a Xenopus double-axis formation assay and a gene expression profile analysis. In human colorectal cancer (CRC) cells, the new compounds JW67 and JW74 rapidly reduced active beta-catenin with a subsequent down regulation of Wnt target genes, including AXIN2, SP5, and NKD1. Notably, AXIN2 protein levels were strongly increased after compound exposure. Long-term treatment with JW74 inhibited the growth of tumor cells in both a mouse xenograft model of CRC and in Apc(Min) mice (multiple intestinal neoplasia, Min). Our findings rationalize further preclinical and clinical evaluation of these new compounds as novel modalities for cancer treatment.

III. Solberg N , Machon O , Krauss S (2008), **Effect of canonical Wnt inhibition in the neurogenic cortex, hippocampus, and premigratory dentate gyrus progenitor pool , Dev Dyn, 237 (7),** 1799-811

Canonical Wnt signaling is crucial for the correct development of both cortical and hippocampal structures in the dorsal telencephalon. In this study, we examined the role of the canonical Wnt signaling in the dorsal telencephalon of mouse embryos at defined time periods by inhibition of the pathway with ectopic expression of Dkk1. Transgenic mice with the D6-driven Dkk1 gene exhibited reduced canonical Wnt signaling in the cortex and hippocampus. As a result, all hippocampal fields were reduced in size. Neurogenesis in the dentate gyrus was severely reduced both in the premigratory and migratory progenitor pool. The lower number of progenitors in the dentate gyrus was not rescued after migration to the subgranular zone and thus the dentate gyrus lacked the entire internal blade and a part of the external blade from postnatal to adult stages.

IV. Machon O , Backman M , Machonova O , Kozmik Z, Vacik T, Andersen L , Krauss S (2007), **A dynamic gradient of Wnt signaling controls initiation of neurogenesis in the mammalian cortex and cellular specification in the hippocampus , Dev Biol, 311 (1),** 223-37

Neurogenesis in the developing neocortex is a strictly regulated process of cell division and differentiation. Here we report that a gradual retreat of canonical Wnt signaling in the cortex from lateral-to-medial and anterior-to-posterior is a prerequisite of neurogenesis. Ectopic expression of a beta-catenin/LEF1 fusion protein maintains active canonical Wnt signaling in the developing cortex and delays the expression onset of the neurogenic factors Pax6, Ngn2 and Tbr2 and subsequent neurogenesis. Contrary to this, conditional ablation of beta-catenin accelerates expression of the same neurogenic genes. Furthermore, we show that a sustained canonical Wnt activity in the lateral cortex gives rise to cells with hippocampal characteristics in the cortical plate at the expense of the cortical fate, and to cells with dentate gyrus characteristics in the hippocampus. This suggests that the dose of canonical Wnt

signaling determines cellular fate in the developing cortex and hippocampus, and that recession of Wnt signaling acts as a morphogenetic gradient regulating neurogenesis in the cortex.

V. Backman M , Machon O , Mygland L , van den Bout CJ , Zhong W, Taketo MM, Krauss S (2005)**, Effects of canonical Wnt signaling on dorso-ventral specification of the mouse telencephalon , Dev Biol, 279 (1),** 155-68

Cre/loxP system in mouse to ablate or activate beta-catenin in the telencephalon in two time windows: before and after the onset of neurogenesis. We show that beta-catenin mediated Wnt signals are required to maintain the molecular identity of the pallium. Inactivation of beta-catenin in the telencephalon before neurogenesis results in down regulated expression of dorsal markers Emx1, Emx2 and Ngn2, and in ectopic up-regulation of ventral markers Gsh2, Mash1 and Dlx2 in the pallium. In contrast, ablation of ss-catenin after the onset of cortical neurogenesis (E11.5) does not result in a dorso-ventral fate shift. In addition, activation of canonical Wnt signaling in the subpallium leads to a repression of ventral telencephalic cell identities as shown by the down-regulation of subpallial markers Dlx2, Nkx2.1, Gsh2, Olig2 and Mash1. This was accompanied with an expansion of dorsal identities ventrally as shown by the expanded expression domains of pallial markers Pax6 and Ngn2. Thus, our data suggest that canonical Wnt signals are involved in maintaining the identity of the pallium by controlling expression of dorsal markers and by suppressing ventral programs from being activated in pallial progenitor cells.

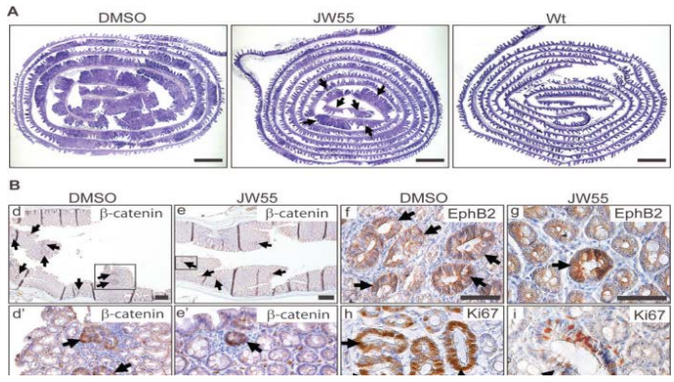

Figure 2. *Tankyrase inhibitor (analogue JW55) treatment decreases development of adenomas in a conditional Apc knockout mouse. A, Representative microscopy images showing hematoxylin and eosin (H&E) stained sections of Swiss-rolls (upper right corner showing the proximal part of ileum) demonstrating an extensive decrease in adenoma development in the small intestine of JW55-treated mice when compared to control mice (DMSO). The right panel shows the morphology of a wild-type (wt) ileum. B, tumors in the colon of* $Apc^{CKO/CKO}$*Lgr5-CreERT2*$^{+}$ *mice displaying high levels of beta-catenin and EphB2 that indicates active Wnt signaling and an ISC-like phenotype. The expression of beta-catenin (d, e), EphB2 (f, g) and the proliferation marker Ki67 (h, i) is shown 1in the colon of vehicle (DMSO) or JW55-treated mice (taken from Waaler, Machon et al... Krauss, 2012).*

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Rognes Group Bioinformatics

Professor Torbjørn Rognes

ABOUT

The Bioinformatics group uses computational methods to analyse nucleotide sequences, amino acid sequences, molecular structures and other molecular data, both to identify new genes of interest and to understand their structure, function and role in the cell. Advanced computational tools are both used and developed. The group is also creating databases and web sites with our tools and generated data. Going forward, our main challenge will be to integrate and make sense of huge datasets for instance generated by new sequencing technologies.

RESEARCH FOCUS

The group has had a long standing interest in identification of novel genes, both protein-coding and non-coding functional RNA genes. How can we predict computationally where transcription occurs in a genome? Is it possible to identify transcribed RNA that possesses important functions without being translated into protein? In the early era of genome sequencing, encoded proteins were of prime importance and RNA genes were almost ignored, but now the non-coding RNAs are of major importance. What about small proteins? For a long time potential proteins less than about 100 amino acids were also almost ignored by gene prediction software because it was so difficult to separate real expressed proteins from hypothetic open reading frames. It is now known that many peptides or short proteins less than 30 amino acids long play important roles.

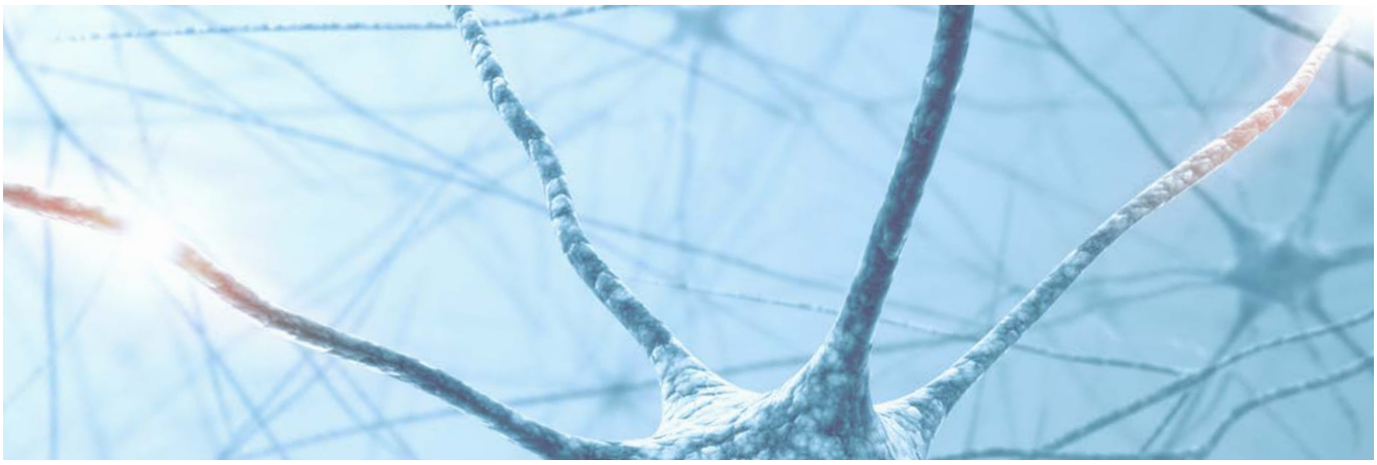
Single nucleotide polymorphisms (SNPs) are a basic form of genome variation that has been well studied in humans. We have been interested in predicting their effects on proteins, as well as in how the different types of SNPs are distributed in the human genome.

We have for long time been involved in identification and characterisation of DNA repair proteins in collaboration with several other CMBN groups. Computational models of the 3D structure of proteins are created and studied in order to understand the molecular mechanisms of enzyme activities. How do 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. We also employ classical sequence analysis methods involving pairwise or multiple sequence alignments, phylogenetic analysis and motif searches in more general applied bioinformatics projects.

We have been interested in the basic algorithms for aligning sequences and for rapid retrieval of similar sequences in a database. These algorithms are fundamental building blocks of more complex bioinformatics applications. It is crucial that they are rapid and accurate in order for the applications to process data efficiently. We have implemented some of these algorithms using different types of parallel computing technology and achieved dramatic increases in speed. We are now working to improve such tools further and to apply them in important cases, like genome assembly, accurate read mapping or variant calling based on data from deep sequencing.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

The group has contributed mainly to two of the visions of CMBN, namely to the fields of DNA repair and of Bio/neuroinformatics. Some of our work also contributes to vision 4, microbiology.



Within vision 1 (DNA repair), we have collaborated with several other groups at CMBN on work package 1 "... the elucidation of novel repair genes and mechanisms" and contributed to a large number of projects where we have identified and characterised DNA repair enzymes as well as some dioxygenases of the AlkB family. In particular, we contributed substantially to the understanding and molecular structure of a new superfamily of DNA glycosylases that include the two Bacillus cereus DNA glycosylases AlkC and AlkD (Alseth et al., ***Mol Microbiol***, 2006; Dalhus et al. ***Nucleic Acids Res***, 2007). See also figure 1.

Within vision 1 of the centre we have also contributed to work package 2 "Ageing, DNA repair and brain function". In an interesting project we studied the CAG repeats characteristic of Huntington disease, and showed that expansion of the repeats seem to occur in two different modes (Møllersen et al., ***PLoS Genetics***, 2009). In this work carried out in collaboration with the group of Arne Klungland, we looked at the distribution of repeat lengths in different tissues and created statistical models that could explain the observations. The expansions are probably induced by DNA repair enzymes.

Naturally, much of our work has been in contribution to CMBN's fifth vision (Bio/neuroinformatics), work package 8, "Basic research and development in bio- and neuroinformatics".

The group has developed RNAmmer, a rapid tool for consistent annotation of ribosomal RNA genes in genome sequences. RNAmmer has recently been established as a standard annotation tool for genome sequencing projects worldwide (Lagesen et al., ***Nucleic Acids Res***, 2007). We have used RNAmmer to study the distribution and heterogeneity of prokaryotic rRNA. This was a collaboration with the group of David W. Ussery at the Centre for Biological Sequence Analysis (CBS) at the Technical University of Denmark.

Furthermore, we have developed methods to design custom oligonucleotide genome tiling microarrays (Thomassen et al., ***PLoS One***, 2009) and used them to study transcription in Escherichia coli subjected to UV-radiation (Thomassen et al., ***PLoS One,*** 2010). These studies where carried out in collaboration with the group of Magnar Bjørås. In collaboration with Rolf Skotheim's group at the Institute of Cancer Research, OUS, custom oligonucleotide arrays have been designed and used to detect oncogenic fusion transcripts (Skotheim et al., ***Mol Cancer***, 2009).

We have looked at known SNPs in all human DNA repair genes and predicted of their effects (Nakken et al., ***Neuroscience***, 2007). Later, we have studied the spectrum of SNPs in human segmental duplications which constitutes a large fraction of the human genome (Nakken et al., ***BMC Genomics***, 2009). We found that a large fraction of SNPs in the dbSNP database were actually invalid because they really represented differences between two copies of a duplicated region in the genome. We also found interesting that there were fewer SNPs in the important guanine bases in human G-quadruplex sequences than elsewere, indicating importance of these sequences (Nakken et al., ***Nucleic Acids Res***, 2009). This work has been carried out in collaboration with Eivind Hovig's group at the Institute of Cancer Research at OUS.

Several tools for rapid alignment and database similarity searches have been developed by the group, including PARALIGN (Sæbø et al., ***Nucleic Acid Res***, 2005) and SWIPE (Rognes, ***BMC Bioinformatics,*** 2011), which is the world's fastest implementation of the important Smith-Waterman local sequence alignment algorithm on an an ordinary computer.

5 SELECTED PUBLICATIONS

I. Saebø PE, Andersen SM, Myrseth J, Laerdahl JK, Rognes T (2005) PARALIGN: rapid and sensitive sequence similarity searches powered by parallel computing technology. Nucleic Acids Res, 33 (Web Server issue), W535-9.

This publication describes the web-based sequence homology search service that we developed based on the PARALIGN similarity search algorithm (Rognes, ***Nucl Acids Res,*** 2001). It is open for anyone and allows for very rapid and accurate searches in a range of different databases. The software is also available for stand-alone use free of charge for academic users and for commercial users through the company Sencel Bioinformatics AS that we established. The software gains its speed from efficient use of parallel computing technology that we have developed further in the new tool SWIPE (Rognes, ***BMC Bioinformatics***, 2011).

II. Dalhus B, Helle IH, Backe PH, Alseth I, Rognes T, Bjørås M, Laerdahl JK (2007) Structural insight into repair of alkylated DNA by a new superfamily of DNA glycosylases comprising HEAT-like repeats. Nucleic Acids Res, 35 (7), 2451-9.

Here we describe the structural model of a completely new, fifth, superfamily of DNA glycosylases. The superfamily includes the two Bacillus cereus DNA glycosylases AlkC and AlkD that we have previously characterised (Alseth et al., ***Mol Microbiol***, 2006). The superfamily consists of an alpha-alpha superhelix fold comprising six HEAT-like repeats and belongs to a larger family of proteins comprised of HEAT-like repeats. The structure, based on homology modelling, reveals a wide, positively charged groove, including a putative base recognition pocket. This groove appears to be suitable for the accommodation of double-stranded DNA with a flipped-out alkylated base. See figure 1 reproduced from this publication for further details. This work was carried out in collaboration with the protein structure group headed by Magnar Bjørås.

III. Lagesen K, Hallin P, Rødland EA, Staerfeldt HH, Rognes T, Ussery DW (2007) RNAmmer: consistent and rapid annotation of ribosomal RNA genes. Nucleic Acids Res, 35 (9), 3100-8.

The publication of new complete genome sequences are usually accompanied by annotations of their genes. In contrast to protein coding genes, genes for ribosomal RNA (rRNA) are often poorly or inconsistently annotated, creating challenges for further research. This publication describes a tool called RNAmmer that contains computational predictors for the major rRNA species from all kingdoms of life. Results from running RNAmmer on a large set of genomes indicate that the location of rRNAs can be predicted with a very high level of accuracy. Novel, unannotated rRNAs was also predicted in many genomes. The software is available as a service at a web server. A large number of genome sequencing projects have used this tool in their annotation effort, which has made this paper the most cited CMBN paper (498 citations as of March 2013).

IV. Thomassen GO, Rowe AD, Lagesen K, Lindvall JM, Rognes T (2009) Custom design and analysis of high-density oligonucleotide bacterial tiling microarrays. PLoS One, 4 (6), e5943.

In this paper, we describe a methodological framework for the design of high-density custom oligonucleotide microarrays based on tiling of bacterial genomes, as well as a framework for analyzing the data generated. Such arrays may be used to study transcription from the genome at a global level. We introduce a novel design method to make two 280,000 feature microarrays each covering the entire genome of E. coli and Neisseria meningitidis. Furthermore, a novel normalization and background estimation procedure for tiling arrays is presented along with a method for array analysis focused on detection of short transcripts. The methods have been applied in our later work on E. coli treated with UV radiation (Thomassen et al. ***PLoS One***, 2010) and MNNG.

V. Nakken S, Rognes T, Hovig E (2009) The disruptive positions in human G-quadruplex motifs are less polymorphic and more conserved than their neutral counterparts. Nucleic Acids Res, 37 (17), 5749-56.

Specific guanine-rich sequence motifs in the human genome have considerable potential to form four-stranded structures known as G-quadruplexes or G4 DNA. The enrichment of these motifs in key chromosomal regions has suggested a functional role for the G-quadruplex structure in genomic regulation. In this work, we have examined the spectrum of nucleotide substitutions in G4 motifs, and related this spectrum to G4 prevalence. Data collected from the large repository of human SNPs indicates that the core feature of G-quadruplex motifs, 5'-GGG-3', exhibits specific mutational patterns that preserve the potential for G4 formation. Furthermore, we provide evidence for a strand bias upstream of human genes.

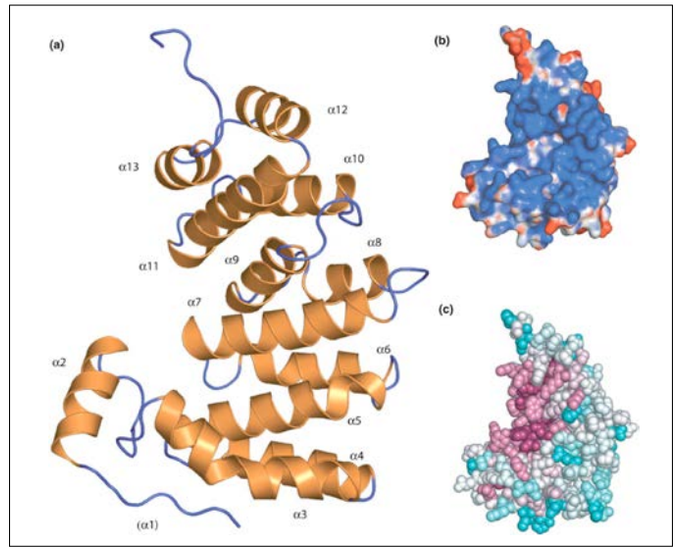


Figure 1. *Structural model with proposed active site and lesion recognition pocket of B. cereus AlkD. The model contains residues 11 through to 226 and is lacking* ***β****-helix* ***β****1 and the 11 C-terminal residues (predicted to be disordered).* ***(a)*** *Cartoon rendering of the protein which comprises 13* ***β****-helices contributing to the six repeats in Figure 2.* ***(b)*** *APBS calculated electrostatic potential mapped onto the protein surface (red = negative, white = neutral and blue = positive) showing the 20–25 Å wide, positively charged, putative DNA binding groove.* ***(c)*** *Amino acid residue conservation in 43 AlkD homologs mapped onto the space filling representation of the model generated with ConSurf. The scale extends from magenta (highly conserved), through white to cyan (highly variable). There is a nest of conserved residues in the putative DNA binding groove, and several conserved basic amino acid residues (Arg and Lys) are sited along the upper and lower edge of the groove. The orientation of the protein in space is identical in all panels.*

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Storm Group
The Brain Signaling Group

Professor Johan F. Storm

ABOUT

Being the only neuro*physiology* group in CMBN, we focus on principles and mechanisms of electrical and molecular signaling in neurons. Such knowledge is essential for understanding how molecules, neurons, and circuits create brain functions, and how these are altered in brain disease, development and ageing. Using electrophysiological, molecular and optical methods, combined with mathematical modeling, our group studies principles and mechanisms for coding and information processing in the cerebral cortex, particularly in glutamatergic neurons and synapses of the hippocampal memory system.

RESEARCH FOCUS

Our group studies how interplay between ion channels and neuromodulation generates electrical signals and dynamics underlying brain states, functions and behaviors, development, ageing, and neurological diseases. Our aims within CMBN: (1) To determine mechanisms and principles underlying the functions of neurons and circuits of the mammalian cortex, in particular how they create and process neural signals. This is fundamental for understanding brain functions and disorders. Research during the last decades has revealed a staggering complexity and new principles of signalling and computations within brain neurons and circuits. Contributing to this new understanding, we determine functional roles and interplay of multiple signalling mechanisms and ion channel types within different neuronal compartments, within each neuron, and in neuronal circuits. (2) To elucidate functional roles of specific neuronal populations, signalling mechanisms and ion channel types, in active neuronal networks *in vivo*, in the brain of behaving animals, especially within the hippocampal memory system. (3) To elucidate roles and therapeutic potentials of neuronal signalling mechanisms in ageing and neurological diseases, including ischemia/stoke, neurodegenerative disorders, epilepsy, and memory disorders. (4) To elucidate the roles of pre- and postsynaptic ion channels of glutamategic synapses and neurons, in particular calcium-activated and other K channels.

ACHIEVEMENTS IN RELATION TO CMBN OBJECTIVES

Our work in CMBN has focused on the *CMBN vision:* "to provide fundamental new insight in the *dynamics and functions of glutamatergic synapses and neurons."* In particular, we made a series of discoveries in relation to WP4, focused on *functions of K^+ channels in glutamatergic synapses and neurons"* (***blue arrows*** in **Fig. 1**, from CMBN's plan). These CMBN plans were based on our previous discoveries that action potentials of glutamatergic neurons in the brain are repolarized by *calcium-activated K^+ channels of the BK type,* and are followed by a sequence of three after-hyper- poarizations (AHPs): fast AHP due to *BK-channels*, medium AHP, due to *KCNQ- or SK-channels*, and slow AHP, due to other *Ca^{2+}-activated K^+ channels*, which also control neuronal excitability and action potential patterns. Such an AHP triad was first described in hippocampal neurons (Storm, ***J Physiol.*** 1987; Storm, ***J Physiol*** 1989; Storm, ***Progr Brain Res*** 1990), and was later found in a variety of brain neurons (cited in international textbooks). These CMBN plans were also based on Storm's previous discovery of the Delay-current *(I_D, Kv1)* in glutamatergic neurons (Storm, ***Nature*** 1988), and his hypothesis (Storm, ***Briain Res*** 1987) that presynaptic *BK channels in glutamatergic synapses can regulate the release of glutamate,* which we later confirmed (Hu et al., *J Neurosci* 2001). Within CMBN, we have mainly contributed to WP4: "calcium-activated K^+ channels (BK and SK channels)...the roles of these... in neuroprotection and...ischemic....and... similar functions of voltage-gated K (Kv) and KCNQ channels."

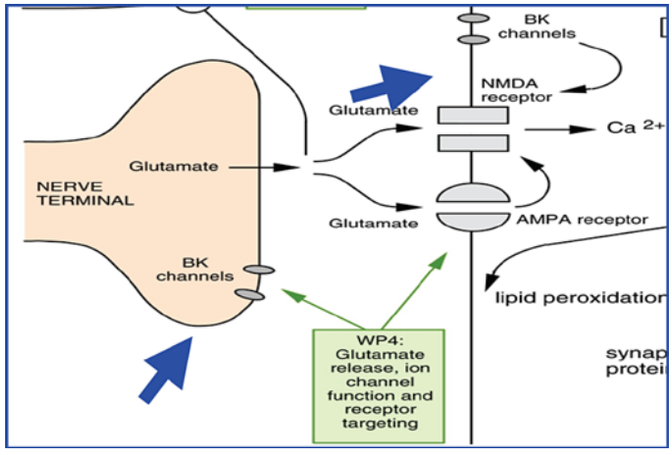


Fig. 1. Glutamate synapse *with pre- and postsynaptic BK-channels (calcium-activated K⁺ channels;* ***blue arrows****). From the CMBN project description, 2001.*

Signaling mechanisms and functions of BK, SK and Kv/KCNQ channels in glutamatergic neurons and synapses. In 2002-2012 we discovered the following mechanisms in mammalian, cortical *glutamatergic neurons and synapses.* In 2002, we discovered that postsynaptic Kv4 K^+ channels regulate long-term synaptic plasticity (LTP) and integration in hippocampal synapses (Ramakers & Storm, ***Proc Natl Acad Sci*** *USA* 99:10144-49). We also found that post-synaptic Kv7/KCNQ channels are essential for frequency-selective responses to oscillating input during memory tasks (*theta resonance*) and that two different forms of *theta resonance* coexist in each neurone (Hu et al. ***J. Physiol*** 545:783-805). By combining double and triple patch clamp recording from dendrites and soma with computational modelling, we later found two segregated mechanisms for filtering of synaptic input: a persisomatic mechanism based on Kv7/KCNQ-channels and persistent Na^+ current, and a dendritic mechanism based on HCN/h channels (Hu et al, ***J Neuroscience*** 29:14472-83). In parallel, we developed a greatly improved, detailed (up to ~5000 compartments) computational model of postsynaptic signaling processes in hippocampal glutamatergic neurons, including the roles of Kv7/*KCNQ channels* (Vervaeke et al., ***Neuron*** 49: 257-270; Hu et al., ***J Neuroscience*** 2009). We also studied presynaptic electrical signalling in glutamatergic axons both computationally and experimentally. We discovered that functional presynaptic Kv7/KCNQ channels exist in glutamatergic axons/synapses and can regulate presynaptic excitability and transmitter release in CA1 area (Vervaeke et al., ***J Physiol*** 676: 235-56) and later extended this finding also to hippocampal, glutamatergic mossy fiber axons (ms. in prep.). We developed a set of novel, detailed, computational models of such axons and presynaptic boutons (hippocampal mossy fibers) and discovered novel functions of presynaptic Kv7/KCNQ channels (m*s in prep for Neuron*; Alle et al, ***Soc Neurosci Abstr*** #42.2, 2009; Storm et al. *FENS Abstr.* 2010; 2009 Murphy et al. *FENS Abstr.* 2010 and 2012). We also confirmed and extended our previous finding in hippocampal glutamatergic neurons that Kv7/KCNQ but not SK channels are essential for postsynaptic after-hyperpolarizations (mAHP) and excitability control (Gu et al., ***J Physiol*** 566: 689-715; Gu et al. ***J Neurophysiol*** 100: 2589-694).

Using transgenic mice with over-expression of dominant negative KCNQ2 subunits, we discovered that Kv7/KCNQ channels in hippocampal glutamatergic neurons are essential not only for the mAHP and theta resonance, but also for *spatial* memory, excitability control and prevention of epilepsy (Peters et al., ***Nature Neuroscience*** 8:51-60) and confirmed that *KCNQ* channel dysfunction leads to epilepsy as described in humans. In 2006-7, we discovered by combined computational and novel experimental (dynamic clamp) techniques, that the *postsynaptic* persistent sodium current paradoxically reduces the frequency gain and modulates spike timing (Vervaeke et al., ***Neuron*** 49: 257-270). We also discovered a novel, paradoxical form of spike frequency adaptation mediated by postsynaptic BK channels in hippocampal neurons (Gu et al. ***J. Physiol.*** 580: 859-82). In 2008-10 we found that postsynaptic SK channels activated by dendritic excitatory synapses regulate their impact (Gu et al. ***J. Neurophysiol.*** 100: 2589-604); and that postsynaptic BK channels are clustered at sites of hypolemmal microdomains and form two distinct pools in a variety of brain neurons (Kaufmann et al, ***J Comp Neurol***, 515: 215–30; Kaufmann et al, ***Neuroscience*** 169: 974-86). Collaborating with Peter Ruth, we discovered that neuronal *BK channels* play a key *neuroprotective* role during and after *brain ischemia, limiting brain infarction and promoting survival after cerebrovascular stroke* (Liao et al., ***Plos One*** 5, e15601, 2010) This fulfils one of the mail goals of CMBN's V2/WP4. Recently we also found that SK channels underlie excitability control in dentate glutamatergic neurons (Moreno & Storm, *Submitted, 2012);* and that Kv1 channels (D-current) changes temporal integration during postnatal development of CA1 glutamatergic neurons. (Giglio & Storm, *Submitted, 2012*).

5 SELECTED PUBLICATIONS

I. Sausbier M, Hu H, Arntz C, Kamm S, Adels-berger E, Sausbier U, Storm JF & Ruth P.
Cerebellar ataxia and Purkinje cell dysfunction caused by Ca^{2+}-activated K^+ channel deficiency. ***Proc Natl Acad Sci USA*** **2004 101, 9474-78**

The roles of BK-channels (large Ca^{2+}-activated K^+ channels) in normal and abnormal brain functions have been largely unknown and are central in the CMBN vision. Using the first knock-out of BK-channels in mice, we discovered that BK channels are essential for normal cerebellar neuronal activity, fast AHP (**Fig. 2**), cerebellar learning, and motor control, and that BK dysfunction leads to cerebellar ataxia.

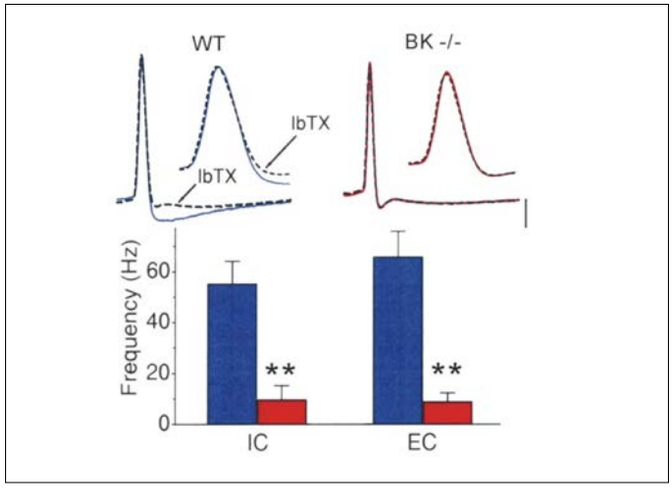


Fig. 2. Functions of post-synaptic BK channels *shown by knock-out of the BK channel gene in mice (BK-/-,* ***blue****), compared to wild type mice (WT,* ***red****): BK channels (blocked by IbTX) generate fAHPs and increase spike frequency in Purkinje neurons. (Sausbier et al. PNAS , 2004).*

II. Liao Y, Kristiansen ÅM, Oksvold CP, Tuvnes FA, Gu N, Rundén-Pran E, Ruth P, Storm JF. Neuronal Ca^{2+}-activated K^+ channels limit brain infarction and promote survival. ***PLoS ONE*** **2010 5(12)**

Building on the hypothesis, proposed by Storm in 1987 (***J Physiol.*** 1987; ***Progr Brain Res*** 1990), that BK channels limit calcium influx and glutamate release, a central point in the CMBN plans (WP4) was to test the roles of "calcium-activated K^+ channels (BK… channels)…in neuroprotection" in ischemia. Using cerebral artery occlusion in BK-channel-KO mice, we discovered that BK channels limit brain infarction, (**Fig. 3**) promote post-infarction survival, and reduce neurological deficits. We also discovered in glutamatergic neurons a novel, surprising form of excitability control performed by BK channels: they facilitate high-frequency firing, thus causing spike frequency adaptation (Gu et al. ***J Physiol*** 2007).

Fig. 3. Neuroprotective effect of BK-channels: *the brain infarct size (white tissue) was far larger in transgenic mice lacking BK channels (BK-/-) than in wild type mice (WT) after occlusion of the middle cerebral artery . From Liao et al. 2010.*

III. H Hu, Vervaeke K, Graham L, Storm JF
Complementary theta resonance filtering by two spatially segregated mechanisms in CA1 hippocampal pyramidal neurons. ***J Neurosci*** **2009 29, 14472-83**

This paper builds on our finding that the medium AHP of hippocampal glutamatergic neurons is due to dual, voltage-dependent mechanisms (Storm ***J Physiol*** 1989). In 2002, we discovered that post-synaptic Kv7/KCNQ channels are also essential for selective responses to oscillating input at *theta* frequencies, which dominate during memory tasks (*theta resonance*), and that two different forms of *theta resonance* coexist in each cell (Hu et al. ***J. Physiol*** 545: 783) (**Fig. 4**, left).

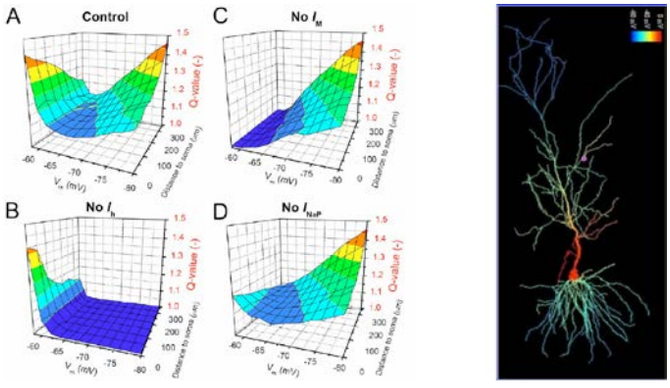


Fig. 4. Dual theta resonance in CA1 pyramidal cells. *Computer simulations of resonance strength (Q-value) in response to oscillatory current, showing two peaks: one somatic at depolarized potentials, due to Kv7 channels, (IM), the other dendritic at hyperpolarized potentials du to HCN (Ih) (Hu et al. J Neurosci 2009)*

By combining double and triple patch clamp recording from dendrites and soma with computational modelling, we found two segregated mechanisms for filtering of synaptic input: a peri-somatic mechanism based on Kv7/KCNQ-channels and persistent Na^+ current, and a dendritic mechanism based on HCN/h channels. In parallel, we developed a greatly improved, detailed, computational model of postsynaptic signalling processes in hippocampal glutamatergic neurons (**Fig. 4**, right).

IV. Peters C, Hu H, Pongs O, Storm JF, Isbrandt D. Conditional transgenic suppression of M channels in mouse brain reveals functions in neuronal excitability, resonance and behavior. *Nature Neuroscience* 2005 *8*, 51- 60.

Using transgenic mice where KCNQ-channels were suppressed by over-expression of dominant negative KCNQ2 subunits, we discovered that Kv7/KCNQ channels in hippocampal glutamatergic neurons are essential not only for the mAHP and theta resonance, but also for spatial memory, excitability control, normal brain development, and prevention of epilepsy. Thus, the mutant mice showed memory loss, loss of the medium AHP, massive increase in neuronal excitability, and epileptic seizures resembling the epilepsy syndrome (dubbed BFNC) in humans with KCNQ mutations. These findings build on our previous findings in isolated hippocampal slices, dissecting the mechanisms of the medium AHP and theta resonance in glutamatergic neurons (Storm ***J Physiol*** 1989; Hu et al. ***J Physiol*** 2002; Hu et al. ***J Neurosci.*** 2007; Hu et al. ***J Neurosci.*** 2009).

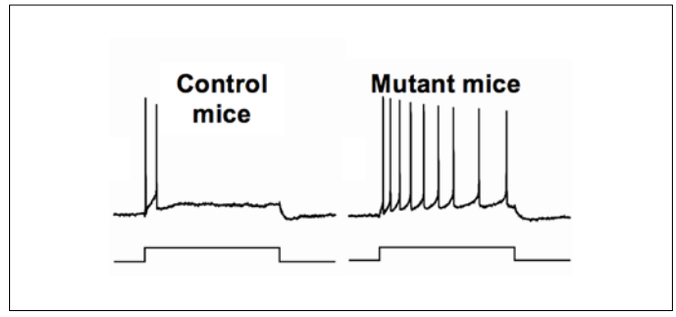


Fig. 5. Transgenic suppression of M channels in reveals their role in neuronal excitability *(Peters et al. Nature Neuroscience, 2005*

V. Vervaeke KGA, Hu H, Graham LJ, Storm JF. Contrasting effects of the persistent Na^+ current on neuronal excitability and spike timing. *Neuron* 2006 *49*, 257- 270

By combining truly predictive computational modeling and a novel experimental application of *dynamic clamp*, we discovered novel, unexpected functions of the postsynaptic persistent sodium (NaP) current in glutamatergic neurons: we found that the NaP current paradoxically enhances the after-hyperpolarizations (AHPs) and reduces spike frequency gain, while it modulates spiking regularity and spike time precision in opposite directions. We first predicted the surprising effects on AHPs and frequency gain (f/I slope) by computational modeling, and only subsequently tested and verified the predictions experimentally by patch clamp recordings from hippocampal glutamatergic neurons. Our novel application of the dynamic clamp technique, for adding and subtracting virtual NaP currents in live cells, was later further described in a chapter (Storm, Vevaeke & Hu, 2009) in the book: *Dynamic-Clamp: From Principles to Applications (Springer Series in Computational Neuroscience*, Eds. Alain Destexhe and Thierry Bal).

MOST IMPORTANT DISCOVERIES FROM THE CMBN RESEARCH GROUPS

Among the key findings in relation to the CMBN core vision is that DNA repair in the cells of the brain, which are mostly non-replicating, is directly implicated in genome instability related to the pathology of neurodegenerative diseases including Huntington's disease. We have also identified roles of nuclear and mitochondrial DNA repair in neurogenesis and neural differentiation. Furthermore, the role of DNA repair and genome maintenance in relation to ageing and mitochondrial function in healthy cohorts and in Alzheimer's disease (AD) mice models and in patients with dementia has been described. One of the fundamental CMBN discoveries is the identification of a novel mechanism for DNA repair by direct reversal. This novel mechanism for DNA repair has been analyzed *in vivo* and its role in the protection against inflammation was recently discovered. CMBN scientists have also provided fundamental new insight in the molecular structure and functions of glutamatergic synapses and neurons, thus paving the way for rational therapeutic strategies targeted to the main excitatory fibre system in the brain. Realizing the fact that neuroglial cells (astrocytes, oligodendrocytes, microglia) are important for neural signalling, is another major breakthrough. Cellular responses in water homeostasis and brain edema and the pluripotency of brain stem cells yield promise for next-generation novel prevention and therapeutics. The CMBN groups will continue their focus on DNA repair in the brain and other organs to further increase the understanding of ageing and important human disease conditions, including AD and other neurodegenerative diseases, cancer and infectious diseases. It is expected that this added insight will develop bridges in translational brain research, and lead to future developments for molecular medicine and diagnostic and therapeutic strategies.

Table 1: The discoveries that the CMBN groups consider their most important through the lifetime of the Centre.

Group	Discovery	Impact	Reference
Genome Dynamics and Pathogenesis Tone Tønjum	*The intragenic distribution of DNA uptake sequences are biased towards DNA repair, recombination and replication genes*	*Transformation of DNA has a predominantly conservative output, rather than mediating variation*	*Nucl Acids Res 32:1050-8, 2004* *Genome Biol 9:R60, 2008* *PLoS One 7(7):e39742, 2012* *PloS Genetics 9: 2013*
Synaptic Neurochemistry Laboratory Linda H. Bergersen / Jon Storm-Mathisen	*Novel functions of neuroglial cells*	*Astrocytes boost synapses* *Oligodendrocytes respond to glutamate and need lactate*	*Nature 438:1162-6, 2005* *Nat Neurosci 10:331-9, 2007* *J Neurosci 31:538-48, 2011* *Cereb Cortex 22:1690-7, 2012*
Neurotransporter Group Niels Chr. Danbolt	*Quantitative assessment of neuronal glutamate transporters*	*EAAT2 mediated uptake in glutamateric terminals is functionally relevant short circuiting the Glu-Gln cycle, while EAAT3 is not involved in synaptic events*	*Neuroscience 157:80-94, 2008* *J Neurosci 32:6000-13, 2012*
Unit for Cell Signalling Stefan Krauss	*A dynamic gradient of Wnt signaling controls initiation of neurogenesis in the mammalian cortex and cellular specification in the hippocampus*	*New understanding of the development of the mammalian forebrain*	*Dev Biol 311:223-37, 2007*
Laboratory of Molecular Biology Magnar Bjørås / Erling C. Seeberg	*DNA glycosylases removing oxidative DNA damage (Ogg1, Neil1 and Neil3) play important roles in triplet expansion and neurogenesis in brain*	*Repair of oxidative DNA damage has a major impact on cognitive function and triplet expansion in neurodegenerative disease*	*Nature 421: 859-63, 2003* *Nature 447:447-52, 2007* *Stem Cell 28:2195-204, 2010* *J Neurosci 31:9746-51, 2011* *PNAS 108:18802-7, 2011* *Cell Rep 2:503-10 2012*
Bioinformatics Group Torbjørn Rognes	*The molecular structure of the AlkC and AlkD DNA glycosylases from Bacillus cereus*	*Shown the existence of a fifth new superfamily of DNA glycosylases*	*Mol Microbiol 59:1602-9, 2006* *Nucleic Acids Res 35:2451-9, 2007*
Molecular Neuroscience Mahmood Amiry-Moghaddam / Ole Petter Ottersen	*Roles of aquaporin water channels in brain physiology and pathology*	*Brain aquaporin AQP4 plays an important role in brain volume and ion homeostasis, and is a molecular target for therapy of acute brain edema*	*PNAS 100:2106-11, 2003* *PNAS 100:13615-20, 2003* *PNAS 108:2563-8, 2011*
Genome Repair and Regulation Arne Klungland	*Identified role of Alkbh2 for removing methylation adducts. Characterized the enzymatic activity of other AlkB homologs*	*Alkb homologs have roles in diseases, including cancer and obesity*	*EMBO J 25:2189-98, 2006* *EMBO J 26:2206-17, 2006* *Cancer Res 68:4142-9, 2007* *Mol Cell Biol 30:1814-27, 2010* *Nat Commun 2:172, 2011* *Mol Cell 49: 18-29, 2013*
Molecular and Cellular Basis of Microbial Pathogenesis Group Michael Koomey	*Multiple bacterial proteins undergo direct, variable modification with O-linked glycans and zwitterionic phosphoform*	*Due to PTMs, the structure, function and antigenicity of bacterial proteins are far more variable than previously recognized*	*PNAS 101:10961-6, 2004* *PNAS 106:4447-52, 2009* *J Bact 192:2816-29, 2010*
The Brain Signalling Group Johan F. Storm	*Perisomatic Kv7/KCNQ and persistent Na+ currents underlie neuronal resonance, excitability and spike timing control, after-hyper-polarizations, spatial learning, epilepsy*	*Sub-threshold currents have important and surprising integration and signaling roles* *(First transgenic suppression of Kv7/KCNQ; first dynamic clamp study of persistent Na^+ current)*	*Nat Neurosci 8:51-60, 2005* *Neuron 49:257-270, 2006.* *J Neurosci 29:14472-83, 2009* *J Neurosci 27:1853 –67, 2007* *J Physiol 566:689-715, 2005*
Neural Systems Laboratory Jan Gunnar Bjålie	*Digital atlasing of gene, molecular, and systems level data in the brain provide a foundation for generation of disease models.*	*Exact knowledge on whole brain distribution of specific genes, molecules and other entities, available through online database applications, shared with the research community.*	*NeuroImage 33: 449-462, 2006* *NeuroImage 14:2603-11, 2011* *PLoS One 6(8):e22669, 2011*

STRATEGY FOR CONTINUATION OF THE CMBN LEGACY

An important key to success: A well-prepared exit / integration strategy. When addressing the CMBN future and exit / integration strategy, we strive to retain the positive consequences of CMBN and to keep the competence on board. When making plans for the future, the solution for CMBN is to follow up the annotated CMBN vision in a frontline science pursuit through multidisciplinary activity in molecular biology, molecular medicine & brain research/aging. An important aim for CMBN is to harvest the benefits of the considerable investments that were made into CMBN during 2003-2012.

The SERTA organization model -- a bottom up strategy. In the contract between RCN and the host institutions UiO and OUS, it is explicitly stated that the host institutions are obliged to take over and maintain the most important competence and infrastructure after the Centre period expire in 2012. To secure the CMBN legacy and ensure that CMBN assets are not lost but are used to maximum benefit in the future, efficient use of CMBN's past advances and discoveries must be maintained. Therefore, a CMBN exit strategy building on CMBN-derived SFFIII applications to RCN has been designed and implemented, enriching the positive outcomes of CMBN. The Faculty of Medicine at UiO has defined a format for the continuation of CMBN as Scientific Excellence Research Thematic Areas (SERTAs) for 5 years, with the prospect of renewal for an additional 5 years. Thereby, a sustainable framework for priority research by CMBN scientists is secured. The three CMBN-derived SERTAs established are entitled SERTA Healthy Brain Aging/SFFIII finalist, SERTA Genome Integrity and SERTA Brain Adaptation. UiO has specifically allocated 2 mNOK per year for two consecutive 5-year periods to secure values and assets generated by CMBN, including competence and human capital, running costs, website and advanced equipment. In addition, the Faculty of Medicine will fund one professor and the Institute of Basic Medical Sciences will fund one senior researcher. The call for the professorship is in the new discipline "Molecular neuroscience". In this way, the key expertise of CMBN is kept on board. UiO and OUS have positively influenced the SERTA implementation and organization.

Table 2: The future focus of the exCMBN groups and their contribution to the new SERTAs.

Group	SERTA name	Main contribution to SERTA
Genome Dynamics and Pathogenesis	*Healthy Brain Aging (HBAC)*	*Impact of infections and inflammation on brain aging and in eliciting brain disease*
Synaptic Neurochemistry Laboratory	*Healthy Brain Aging*	*Glial cell biology* *Physical exercise – brain health* *Ultrastructural quantification*
Molecular and Cellular Basis of Microbial Pathogenesis Group	*Healthy Brain Aging*	*Comparative genomics in N. meningitidis and related clades*
Molecular Neuroscience	*Healthy Brain Aging*	*Role of astrocyte in maintenance of a healthy brain and development of ageing related brain diseases (astrodegenerative brain disorders)*
Neural Systems laboratory	*Healthy Brain Aging*	*Brain atlasing systems for animal models of disease and aging* *Neuroinformatics systems for data management, analysis, and dissemination*
Bioinformatics group	*Centre for Genome Integrity (CGI)*	• *Bioinformatics competence in general* • *Advanced analysis of large molecular datasets using computational and statistical methods* • *Development of new or improved bioinformatic methods.*
Laboratory of Molecular Biology	*Centre for Genome Integrity*	*Impact of oxidative DNA damage on cognitive function in brain.*
Genome Repair and Regulation	*Centre for Genome Integrity*	*Identify novel epigenetic marks.* *Unravel the role of reversible RNA methylation in reprogramming and disease.*
Neurotransporter Group	*Developing and Adaptive Brain (DAB)*	*Roles of glutamate and GABA transporter proteins*
The Brain Signaling Group	*Developing and Adaptive Brain*	*Neuronal and circuit signaling and dynamics in relation to brain functions, development and plasticity*

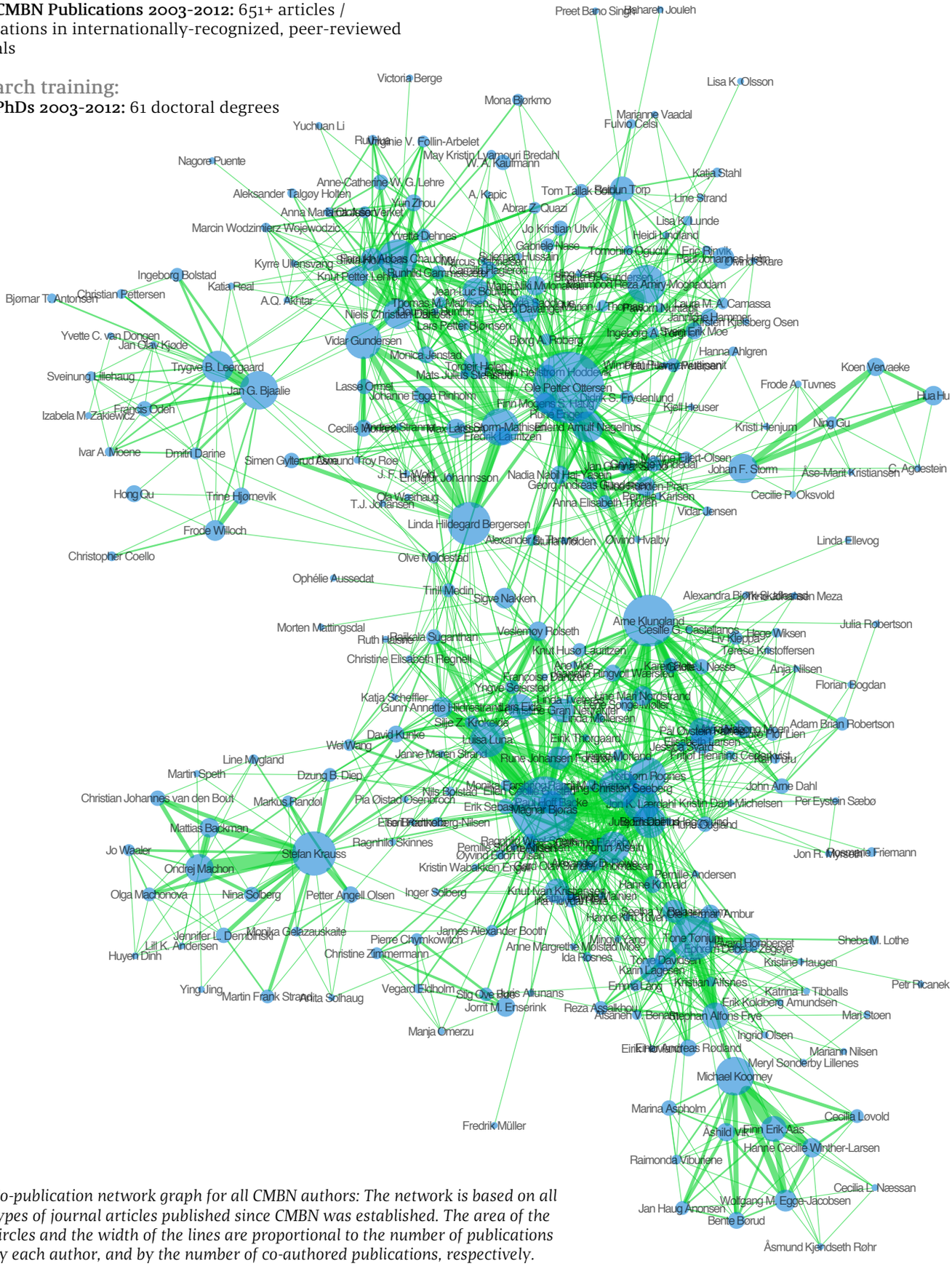
AUTHOR NETWORK

Publications:

Total CMBN Publications 2003-2012: 651+ articles / publications in internationally-recognized, peer-reviewed journals

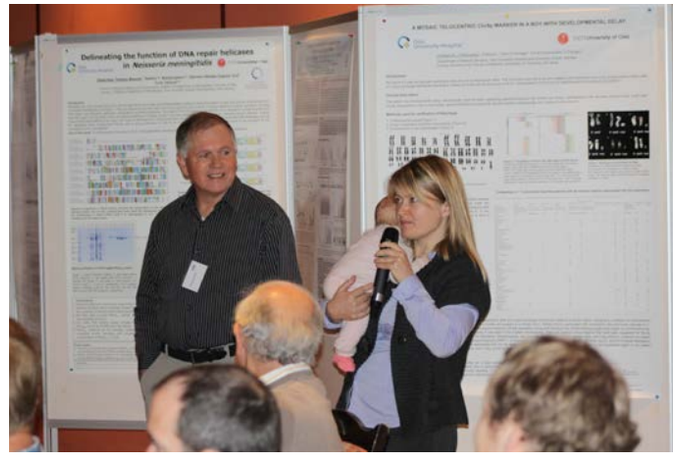
Research training:

Total PhDs 2003-2012: 61 doctoral degrees



Co-publication network graph for all CMBN authors: The network is based on all types of journal articles published since CMBN was established. The area of the circles and the width of the lines are proportional to the number of publications by each author, and by the number of co-authored publications, respectively. Figure created using Publika and Cytoscape.

Publications



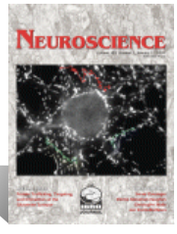
PUBLICATIONS 2012

CMBN Special Issues – tools to promote frontline interdisciplinary science:

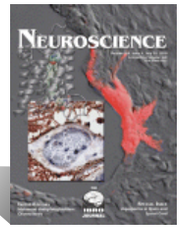
Genome dynamics shaping neuroscience. Special issue based on the GDN4 meeting, in Mech. Age. Dev. Edited by Juel-Rasmussen, Shiloh, Bohr & Tønjum.

The role of genome instability and DNA repair in neurodegenerative disease, Neuroscience 2007. Edited by Bohr, Ottersen & Tønjum.

Microbial Genome Dynamic, FEMS Microbiology Reviews 2009. Edited by Casadesus, Bayliss, Rocha & Tønjum.

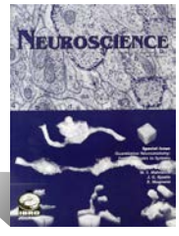


Protein trafficking, targeting, and interaction at the glutamate synapse. Neuroscience 2009. Edited by Davanger, Manahan-Vaughan, Mulle & Storm-Mathisen.



Aquaporins in the Brain and Spinal Cord. Neuroscience 2010. Edited by Amiry-Moghaddam & Nesic.

From Cochlea to Cortex: Recent Advances in Auditory Neuroscience. Neuroscience 2008. Edited by Malmierca, Storm-Mathisen & Cant.



Quantitative Neuroanatomy: From Molecules to Systems - A special issue in honor of the late Professor Theodor W. Blackstad. Neuroscience 2005. Edited by Bjaalie.

Brain Water Homeostasis. Neuroscience 2004. Edited by Agre, Nielsen & Ottersen.

CMBN and the Public

CMBN AND THE PUBLIC SUMMARY 2012

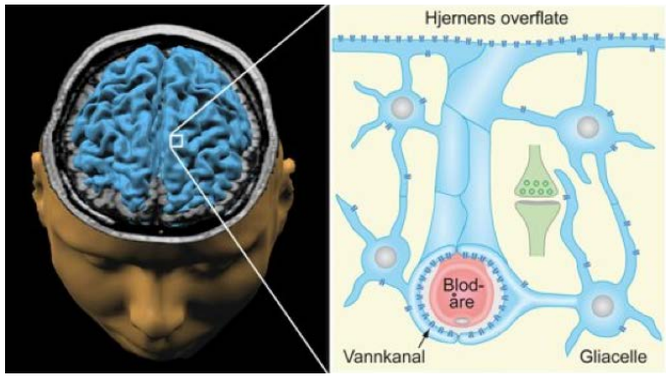
Important Brain Discoveries
International Business Times 26. November 2012

Modellerer signalkaos i hjernen
Apollon, 13 September 2012

Forklarer hjernens avfallsmekanisme
Dagens medisin, 11 September 2012

Vannkanaler renser hjernen
forskning.no, 5 September 2012

Vannkanaler holder hjernen ren
Nyheter om Nevronor, Norges forskningsråd, 11 September 2012



Vannkanalene finnes i gliacellene og er spesielt tallrike langs hjernens overflate og rundt blodårer. (Illustrasjon: E. A. Nagelhus og G. F. Lothe. MR-bilde: K. E. Emblem, Rikshospitalet, og I. Rasmussen, Nidelven hjerneforskningslaboratorium)

Melkesyre beskytter hjernen Aftenposten, 25 January 2012
Also published in **Bergens Tidende, Adresseavisen, Stavanger Aftenblad and Fædrelandsvennen.**

Skader i genene bestemmer om du får kreft ABC Nyheter, 22 January 2012

Are stiff muscles good for your brain?
News from Nansen Neuroscience Network, 5 January 2012

Enzymmangel gir sykdom
Forskningsaktuelt, Institutt for klinisk medisin, Det medisinske fakultet, UiO, 5 January 2012

Det spirer og gror i hjernen
Morgenbladet, 26 Januar 2012

Gode vibrasjoner
Morgenbladet, 26 April 2012

Overraskende hjerneceller
Morgenbladet, 21 Juni 2012

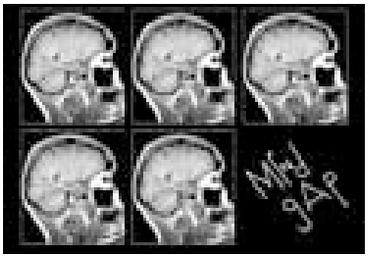
Suger strøm fra mikrokontakter i hjernen
forskning.no, 4 Desember 2012

Leif Gjerstad and Tone Tønjum in discussion with MS patient Inngun Aa from the Monsen expedition Ingen grenser.

MINDGAP / HJERNELØRDAG

The exhibition MindGap at the Technical Museum of Oslo, edited by world famous US artist Robert Wilson, is about the brain and brain research. It was open April 16, 2011 - December 31, 2012. CMBN was central in the planning and scientific content of the exhibition and has also contributed economically. The UiO was the main partner for the exhibition, and the exhibition was part of the 200th anniversary of the founding of the University of Oslo (Norway's first university).

CMBN has also contributed to "Brainy Saturday"/"Hjernelørdag" organized by our collaborators in the Norwegian Brain Council in connection with the MindGap exhibition. Researchers from CMBN have demonstrated dissection of pig's brains and talked about brain disease and neuroscience research, an activity that has been very well received by the public.



CMBN PhDs

A total of 65 PhD's were defended by CMBN graduate students 2003-2012.

2013

Petr Ricanek
Characterization of clinical, microbial and epithelial barrier parameters in newly diagnosed IBD patients
Faculty of Medicine, University of Oslo, 1 March 2013
Supervisor: Andreas Rydning and Tone Tønjum

Ida Rosnes
Structure and Dynamics of Endonuclease V Interacting with DNA
Faculty of Medicine, University of Oslo, 28 February 2013
Supervisor: Magnar Bjørås

Silje Zandstra Krokeide
Biochemical characterization of mammalian NEIL3 and involvement in repair of hydantoin lesions in proliferative tissue
Faculty of Medicine, University of Oslo, 26 February 2013
Supervisor: Magnar Bjørås

Martin Frank Strand
Modulating the Hedgehog pathway
Faculty of Medicine, University of Oslo, 18 January 2013
Supervisor: Stefan Krauss

2012

Yngve Sejerstedt
Neil3 DNA Glycosylase in Maintenance and Repair of the Mammalian Brain
Faculty of Medicine, University of Oslo, 5 December 2012
Supervisors: Ola Didrik Saugstad and Magnar Bjørås

Yun Zhou
GABA transporters- distribution and functional roles
Faculty of Medicine, University of Oslo, 1 Desember 2012
Supervisor: Niels Christian Danbolt

Yngve Thomas Bliksrud
Hereditary tyrosinaemia type I. Studies on the molecular genetics and DNA repair enzymes
Faculty of Medicine, University of Oslo, 30 November 2012
Supervisor: Magnar Bjørås

Kari Furu
Genetic and epigenetic regulation in spermatogenesis in mice; lessons from Alkbh1 and Tzfp mutants
Faculty of Medicine, University of Oslo, 29 November 2012
Supervisor: Arne Klungland

Kristian Alfsnes
Meningococcal genome dynamics: conservation and variability in Neisseria meningitidis
Faculty of Medicine, University of Oslo, 1 November 2012
Supervisor: Tone Tønjum

Toril Ranneberg-Nilsen
The impact of DNA base excision and chromatin remodeling on cytomegalovirus DNA-replication
Faculty of Medicine, University of Oslo, 4 September 2012
Supervisors: Magnar Bjørås and Halvor Rollag

Hanne Korvald
Repair of alkylation induced DNA damage in Schizosaccharomyces pombe
Faculty of Medicine, University of Oslo, 13 June 2012
Supervisor: Ingrun Alseth

Line Nilsen
Repair of AP sites in Schizosaccharomyces pombe
Faculty of Medicine, University of Oslo, 5 June 2012
Supervisor: Magnar Bjørås

Chang Cheng
Monocarboxylate Transporters in Tumor Cells and Mitochondrial DNA Toxicity Mice
Human Anatomy, Basic Medical School, Zhengzhou University, P.R. China, 24 May 2012
Supervisors: Linda H. Bergersen, Xiaoqun Gao

Fredrik Lauritzen
Monocarboxylate transporters in temporal lobe epilepsy
Faculty of Medicine, University of Oslo, 26 April 2012
Supervisor: Linda Bergersen

Rune Ougland
Role of the mammalian AlkB homologs 1 and 3 in RNA repair and epigenetic regulation of stem cell differentiation and development
Faculty of Medicine, University of Oslo, 29 March 2012
Supervisor: Arne Klungland

Cecilie Morland
Amino Acid Neurotransmission and its Regulation by Valproate: Focus on Aspartate
Faculty of Medicine, University of Oslo, 9 March 2012
Supervisor: Vidar Gundersen

Nadia Nabil Haj-Yasein
Roles of aquaporin 4 and Kir4.1 in brain water and potassium homeostasis: lessons from knockout mice
Faculty of Medicine, University of Oslo, 28 February 2012
Supervisor: Erlend Arnulf Nagelhus

Silvia Holmseth
Glutamate transporters around the tripartite synapse
Faculty of Medicine, University of Oslo, 17 January 2012
Supervisor: Niels Christian Danbolt

CMBN events 2012

CMBN ACTIVITIES

CMBN has invested in advanced courses and symposia, engaging outstanding lecturers from Norway and abroad. The philosophy is practiced that the Centre's PhD students and postdoctoral fellows shall be exposed to the international leaders in the field, and this will be promoted through activities such as the PhD group, the postdoc group and "Meet the speaker" / "Host the speaker" events. In addition to the symposia and courses, the Centre has organized frequent CMBN lectures. Only top tier researchers can qualify as CMBN lecturers and these have been invited on the premise that they shall contribute to the education of the PhD students of the Centre. Obviously, the PhD training is a major responsibility also for the CMBN guest professors, who spend several weeks at CMBN every year and contribute to symposia and other activities.

ERLING SEEBERG SYMPOSIUM

The Erling Seeberg symposium has been organized three times with support from CMBN. The first meeting was in Bodø and Henningsvær (2006), the next meeting in Ålesund and Geiranger (2009) and the last meeting in Trondheim and Ørlandet (2012). One of the motivations for organizing these meetings was to honor Erling Seeberg. He made many important and novel contributions to the field of molecular biology in general and DNA repair and mutagenesis specifically. The main scientific focus has been on recent advances that provides mechanistic understanding of specific repair pathways and the area of DNA damage response. In the spirit of Erling Seeberg the organizers have emphasized personal interactions and open discussions about new ideas and preliminary results to nourish the ideas of science creating friendship and cooperation. The meeting have been very successful and we are planning the next meeting in 2015.

SEMINAR: SCIENCE AND CAREER DEVELOPMENT

May 10th 2012 CMBN hosted an event called "Science and career development" at the Norwegian Academy of Science and Letters (DNVA). 60 scientists of all ages were gathered to exchange experiences regarding career development. Senior and junior scientists from all over the world gave talks about their science and their way to a research position, giving tips to the audience about how to succeed.

DOPAMINE DISCOVERY DAY

The CMBN symposium "Dopamine Discovery Day" was organized by Linda H. Bergersen and Vidar Gundersen. While dopamine was not discovered in one day we took the opportunity of the 55th anniversary to highlighting recent advances in research on dopaminergic mechanisms.

Dopamine mediates brain mechanisms underlying fundamental and diverse behavioral phenomena such as pleasure, joy, love, motivation, habits and motor control, but dopaminergic dysfunction may lead to dyskinesia, addiction, compulsiveness or psychosis. Speakers were Professor Alain Dagher from Montreal Neurological Institute and McGill University, Montreal QC Canada, Professor Edward Fon also from McGill University Professor Albert Gjedde the Panum Institute, University of Copenhagen and Professor Øivind Hvalby from Department of Physiology, IMB, University of Oslo.

The Norwegian Academy of Science and Letters (DNVA), Oslo, Norway

CMBN ORGANIZES THE FIRST SCIENTIFIC MEETING IN THE NEW PREMISES OF THE ACADEMIA LEOPOLDINA IN HALLE, GERMANY

On June 7-8, 2012 CMBN and the Federation of European Microbiological Societies (FEMS) organized the first scientific event in the new premises of the German National Academy of Sciences Leopoldina in Halle, Germany. The Coinfections 2012 Meeting addressed recent advances in our understanding of polymicrobial infections, synergies between microbes and relevant aspects of symbiosis.

CMBN SYMPOSIUM ON GLIO- AND NEUROTRANSMITTERS

"Glio- and neurotransmitters: significance in brain disease" organized by Linda Hildegard Bergersen and Jon Storm-Mathisen.

The CMBN Symposium "Glio- and neurotransmitters: significance in brain disease" was arranged at the Norwegian Academy of Science and Letters 10th of February 2012. The purpose of the meeting was to highlight recent findings in transmitter signaling in white and grey matter in the healthy and pathological brain. The invited speakers came from different parts of the world and presented state-of-the-art knowledge from basic to clinical science.

External speakers were: Professor Victor Nadler from Duke University in Durham, Professor Albert Gjedde from the Panum Institute in Copenhagen, Denmark, Professor Anders Björklund from Lund University in Sweden, Professor Espen Dietrichs from Oslo University Hospital, Norway, Professor David Attwell from University College London, UK, Professor Vidar Steen, University of Bergen, Norway and Professor Robert Edwards, University of San Francisco, USA.

CELEBRATION OF THE 10TH ANNIVERSARY OF THE CMBN

On October 18th 2012 the CMBN hosted a seminar to celebrate the 10th Anniversary of the CMBN. The CMBN group leaders presented their most important work from the last 10 years and the Norwegian Research Council and the host institutions presented their view on large scientific projects. The seminar was the first to be held in Rotunden in the new Domus Medica annexe. The same evening, CMBN employees and special guests celebrated the event with a dinner and dance at Gamle Losjen.

CONFERENCE SERIES

Conference: 4th Genome Dynamics in Neuroscience Meeting (GDN4)

Genome Dynamics in Neuroscience (GDN) is a conference series that was initiated by CMBN in Oslo in 2006. The conference series has since been hosted by Cynthia McMurray and George Martin in Asilomar, California, USA 2008 and by Keith Caldecott and Peter McKinnon in Brighton, England 2010.

The fourth Genome Dynamics in Neuroscience Meeting (GDN4) was coorganized by the Centre for Molecular Biology and Neuroscience (CMBN) and the Center for Healthy Aging (CEHA). The conference was held at Holmenkollen Park Hotel in Oslo, Norway on September 19th to 22nd 2012. It was the fourth in a series of international meeting addressing genome instability and DNA repair in the context of neuroscience and aging in a multidisciplinary setting.

The objective of the meeting was to highlight key aspects of DNA damage and repair in aging, neurodegeneration and the pathogenesis of neurological disease, and to improve our understanding of how nerve cells communicate in the healthy and diseased brain. Topics that were addressed are relevant for, genome dynamics and maintenance, epigenetics, bioenergetics, stem cell biology, brain development, microbial model systems and synaptic communication. The long-term goal is to understand the molecular mechanisms in the pathogenesis of neurological and complex diseases and identify new approaches for the early diagnosis and treatment of brain disease and age-related neurological impairment.

The conference brought together world-leading scientists to discuss the state-of-the-art and current perspectives on the role of genome instability and DNA repair of normal brain ageing and in the pathogenesis of neurodegenerative diseases. A special issue in the journal Mechanisms of Ageing and Development entitled "Genome Dynamics Shaping Neuroscience" is a by-product of the meeting. Furthermore, 2 young investigator presentations were selected and 3 poster prizes were awarded based on the 20 poster abstracts submitted and presented. See also the GDN4 website: www.gdn4.com The fifth Genome Dynamics in Neuroscience Meeting (GDN5) will be arranged by CEHA in Copenhagen together with CMBN scientists in June 2014.

Fabian Stang, Mayor of Oslo, Lene Juel Rasmussen, Center leader, Center for Healthy Aging (CEHA), Copenhagen, and Tone Tønjum, Center leader, Centre for Molecular Biology and Neuroscience (CMBN), Oslo

Reception at the Oslo City Hall.

Conference room at Rica Holmenkollen Park Hotell

AWARDS AND PRIZES

As an additional measure of impact, prizes have been bestowed on several CMBN scientists. Three CMBN scientists were awarded the Jahre Prize: Erling Seeberg (2004), Jon Storm-Mathisen (2006), and Ole Petter Ottersen (2008). Farrukh A. Chaudhry and Mahmood Amiry-Moghaddam received the Jahre Prize for young investigators in 2006 and 2008, respectively. Ole Petter Ottersen and Jon Storm-Mathisen shared the Lundbeck Prize for 2005. It also deserves mention that Farrukh A Chaudhry, Mahmood Amiry-Moghaddam and Tonje Davidsen were awarded the King's Gold Medal for their PhD theses. The GLs have received a number of other prizes and continually receive invitations to give lectures or arrange symposia at high profile international meetings.

Ole Petter Ottersen holds his presentation

Farrukh Chaudhry and Jon Storm-Mathisen received the Jahre Prize in 2006

The winners of the 2008 Jahre Prize: Amiry-Moghaddam, Ottersen and Taipale

Tonje Davidsen received the King's Gold Medal for her PhD thesis in 2006

Erling Seeberg received the Jahre Prize in 2004

CMBN GUEST PROFESSORS

The Centre has appointed a series of guest professors of high international standing who have worked in the Centre for periods of time on a regular basis and have acted as ad hoc advisors for the Centre. It has been the policy of the Centre to forge alliances with the leading groups in the respective fields of research. Some of the collaborating groups are formally affiliated with the Centre, as CMBN guest professors. These guest professors also function as an informal scientific advisory board SAB) for the Centre. Therefore, in view of the adopted organizational model and expertise of the CMBN board, the management of the Centre has considered it unnecessary to establish an additional SAB.

1. Peter Agre, Professor and Nobel Prize winner in Chemistry, 2003, Johns Hopkins University, Baltimore, USA (http://www.dukehealth.org/AboutDuke/Administration/Administrators/MedicalCenter/PAgr) Funded by RCN and CMBN.

2. Vilhelm A. Bohr, Chief of Laboratory of Molecular Genetics, National Institute on Aging, NIH, 5600 Nathan Shock Drive, Baltimore MD (http://www.grc.nia.nih.gov/branches/irp/vbohr.htm)

3. David Ussery, Associate professor in the Centre for Biological Sequence Analysis, Technical University of Denmark (http://www.cbs.dtu.dk/staff/dave/)

4. Shankar Subramaniam, Professor of Bioengineering, Chemistry and Biochemistry at the University of California at San Diego, and Senior Fellow at the San Diego Supercomputer Center (http://www-chem.ucsd.edu/Faculty/bios/subramaniam.html)

5. Farrukh A. Chaudhry, Associate professor at the Biotechnology Centre, University of Oslo (http://www.biotek.uio.no/research_groups/chaudry_group.html)

6. Pål Falnes, Professor at the Institute of Molecular Bioscience, University of Oslo (www.imbv.uio.no/bkm/groups/falnes/db03-groupmembers/internet/html/nr000010.html)

7. Karl Peter Giese, Professor of Neurobiology and Mental Health, Centre for the Cellular Basis of Behaviour, King's College London

8. Tore Eid, Director, Human Brain Microdialysis Program, Assistant Director, Clinical Chemistry Laboratory, Yale School of Medicine - New Haven Hospital (http://labmed.yale.edu/people/tore_eid.profile)

9. Rolf Sprengel, Molecular Neurobiology, Max Planck Institute for Medical Research, Heidelberg (http://www.mpimf-heidelberg.mpg.de/groups/sprengel)

RECRUITMENT OF YOUNG SCIENTIFIC INVESTIGATORS

Selected young scientific investigators who have expressed a wish to become independent PIs and to apply for ERC funding, but did not yet have their own funding, have been supported with one year of salary ("ventelønn"). CMBN young investigators who have received this support are:


Linda H. Bergersen


Bjørn Dalhus


Torgeir Holen


Ole Herman Ambur

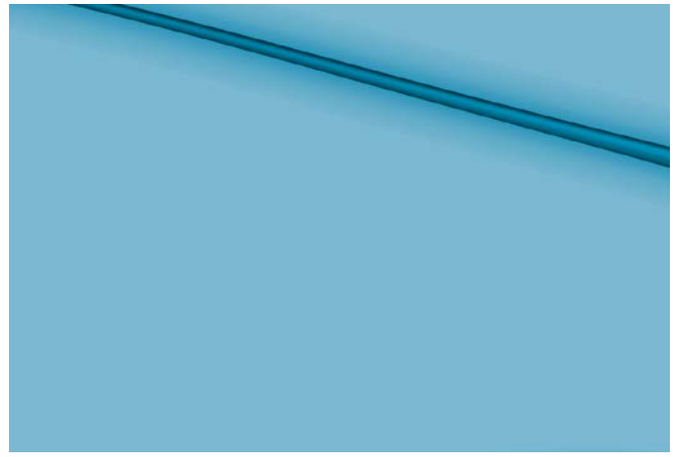

Elisabeth Larsen

RESEARCHER TRAINING: CMBN IS A RESEARCH SCHOOL (FORSKERSKOLE) AT UIO

The Centre has invested heavily in the development of programs for graduate and postgraduate teaching. It is the Centre's policy that all courses and all lectures under the auspices of the Centre shall be open to all researchers – also those coming from the other universities. CMBN has been appointed as an approved Research School ("Forskerskole") at the University of Oslo and CMBN courses have merited points for students who are in PhD training.

CMBN members contribute to the annual interfacultary Master and PhD course in Advanced Neurobiology (MBV4340/9340), given at the Faculty of Mathematics and Natural Sciences with CMBN group leader Johan F. Storm as a main organizer. The CMBN is a partner in the Norwegian Research School in Neuroscience (NRSN), which was funded by the RCN in 2012.

Publications



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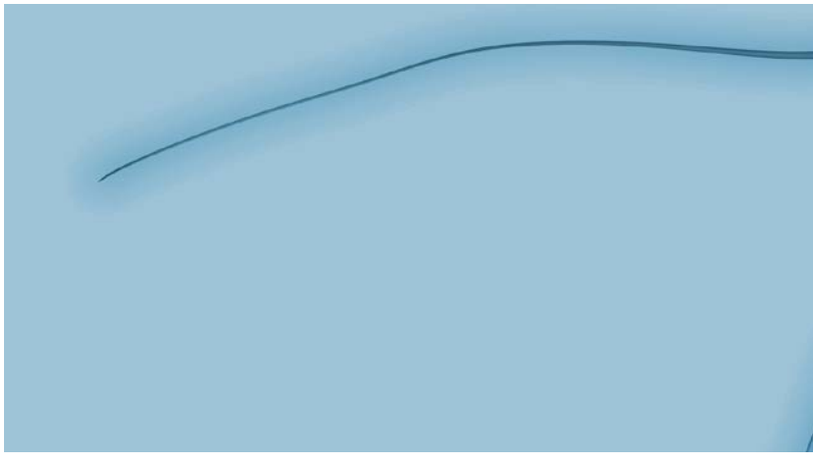
Høydepunkter i 2012

populærvitenskapelig fremstilling

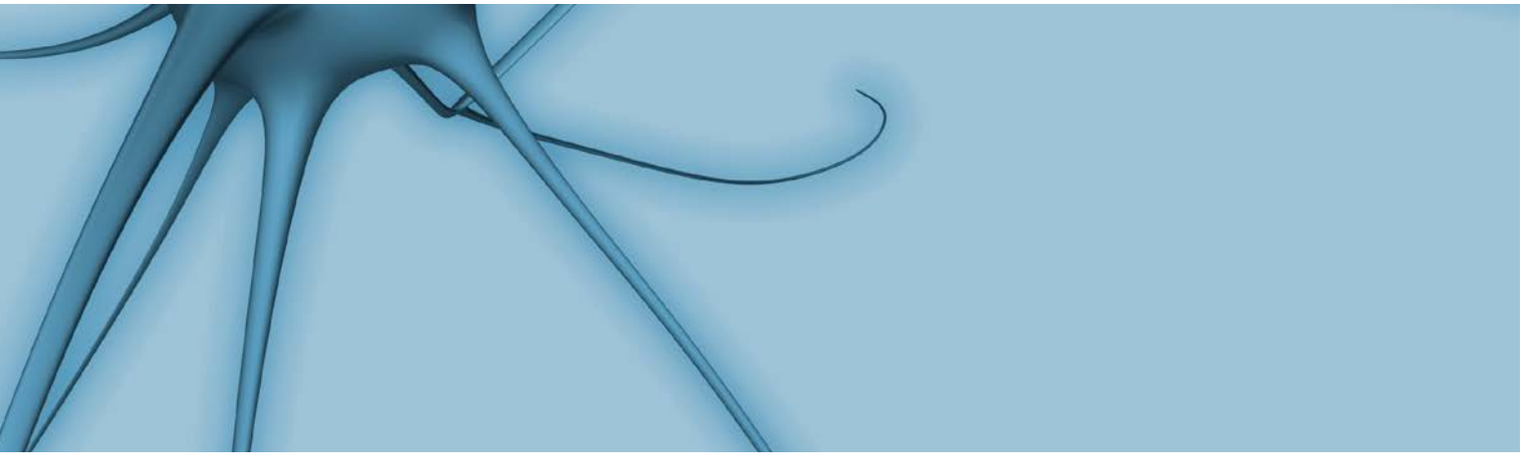


Det viktigste målet for CMBN er å gjøre eksellent forskning fremragende, ved å sikre kvalitet. Ved CMBN er det i 2012 gjort en rekke oppdagelser og funn som er sentrale i forhold til den faglige visjonen om å forstå hvordan nerveceller kommuniserer med hverandre og hvilken rolle skader i arvestoffet spiller for aldring og utviklingen av nevrologiske sykdommer. I våre celler skjer det hver dag betydelige skader på arvestoffet (DNA). Slike skader skjer også i hjernecellene, som utgjøres av nerveceller (nevroner) og støtteceller (gliaceller). Hovedmassen av nervecellene deler seg ikke, derfor er det spesielt viktig at de vedlikeholdes godt. Forskning på disse prosessene utgjør kjernevirksomheten ved CMBN. Forskere ved CMBN har oppdaget en ny link mellom Huntingtons sykdom og DNA-reparasjon ved å identifisere et DNA-reparasjonsgen som modifiserer CAG triplett-instabilitet i huntingtin-genet (***Hum Mol Gen*** 2012). Huntingtons sykdom er en progressiv neurodegenerativ sykdom forårsaket av ekspansjon av CAG:CTG-elementer i genet som koder for det polyglutamin-holdige proteinet huntingtin, som vist i tidligere studier fra CMBN (***Nature*** 2007).

Hjerneceller har et livslangt ansvar for at vår hjerne fungerer som den skal. Når reparasjonen ikke går som normalt, endres DNA og vi kan få sykdommer i nervesystemet, som for eksempel Alzheimers sykdom. Det viser seg imidlertid nå at stamceller i hjernen har evne til å erstatte skadde nerveceller og gjenvinne hjernefunksjon etter hjerneskade. Stamcelleaktivitet i hippocampus hos voksne ivaretas ved Neil3-avhengig DNA-reparasjon av oksidative skader (***Cell Rep*** 2012). Nok en nyvinning er gjort i studiet av hvor viktige stamceller er for reparasjon i hjernen, idet AlkB homolog 1 (ALKBH1) er vist å være en histon-dioxygenase som virker spesifikt på histon H2A, et av proteinene som 'pakker inn' DNA. Når Alkbh1 mangler i embryonale stamceller, blir det oppregulering av gener som styrer stamcellens evne til å utvikle seg i forskjellige retninger, og ALKBH1 virker under tidlig celle-differensiering og utvikling av nervesystemet ved å metylere histon H2A (***Stem Cells*** 2012). Nye oppdagelser er også gjort på analyse av molekylær struktur og funksjon av modifisert DNA (***Nature Prot*** 2012) og av komponenter som utfører DNA binding og prosessering (***Structure*** 2012; ***PLoS One*** 2012; ***DNA Repair*** 2012; ***Nucl Acid Res*** 2012; ***Microbiol*** 2012). Samtidig har genekspresjonprofilen for DNA-reparasjon i en musemodell for Alzheimers sykdom vist invers ekspresjon av DNA-glykosylasen OGG1 og APE1 i hjernevev, som respons på den store graden av oksidativt stress som oppstår idet hjerneplakk dannes (***ICAD*** 2012).

Vannbalanse er spesielt viktig i hjernen, som må ha konstant volum for å få plass inne i hodeskallen, og reguleres av vannkanaler kalt aquaporin-4 (AQP4). CMBN-forskere har gjort en rekke oppdagelser på AQP4-lokalisering, -funksjon og -interaksjoner, som regulerer gliacelle-osmolaritet og ionefluks (***PNAS*** 2012; ***Glia*** 2012). Det er glia-cellene som kontrollerer bevegelse av vannmolekyler gjennom blod-hjernebarrieren og "skyller" hjernen fri for avfall (***Science Transl Med*** 2012), noe som representerer en tidligere ukjent sirkulasjonsvei for væske i hjernen. Denne sirkulasjonen har en rensende funksjon på linje med lymfesystemet ellers i kroppen.

Blant gjennombruddene i 2012, har CMBN-forskere oppdaget nye mekanismer i genomdynamikk og evolusjon hos bakterier (***PloS One*** 2012; ***Microbiology*** 2012), mens struktur, funksjon og ekspresjon membranproteiner som for eksempel sekretiner og andre virulensfaktorer har blitt karakterisert (***PloS Pathogens*** 2012; ***EMBO Mol Med*** 2012).



Det er gjort nye funn i mekanismene for hjernesignalering, med tallrike observasjoner på glia- og nevrotransmittere og deres signalering og betydning ved hjernesykdom (***Glia*** 2012; ***Cereb Cortex*** 2012; ***J Neurosci*** 2012; ***J Histochem*** Cytochem 2012). Det er vist at både glukose og laktat regulerer utvikling og myelinisering av glia-oligodendrocyte (***Nature*** 2012; ***Glia*** 2012; ***Cereb Cortex*** 2012). Det er også utviklet et tre-dimensjonalt atlas over rottehjernen, som viser hvordan hjerneceller kan virke sammen i nettverk (***Front Neuroinform*** 2012). Oppbyggingen av elektroniske hjerneatlas viser at man kan forstå hjernen bedre ved bruk av nevroinformatikk (***Neuroimage*** 2012; ***Front Neuroinform*** 2011).

Andre viktige oppdagelser gjelder mitokondrienes betydning for aldring og nevrodegenerative sykdommer. Bioenergetikk og mitokondriefunksjon henger uløselig sammen. Mitokondrielle DNA-skader fører til nedbrytning og død av celler, noe som også gjelder nevroner og gliaceller og derved karakteriserer nevrodegenerative sykdommer. Mitokondrier genererer cellens energi og er viktige for nervevev som har et høyt energibehov. Mitokondrie-DNA (mtDNA) inneholder gener som koder for deler av elektrontransport-kjeden, hovedsetet for den mitokondrielle energiproduksjonen. Studiene understreker betydningen av å opprettholde intakt mtDNA for å unngå tap av mitokondriell funksjon (***DNA Repair*** 2012). Det har skjedd ytterligere framskritt i forståelsen av hvordan cellens byggestener dekoreres posttranslasjonelt med sukker/karbohydrater (***Mol Microbiol*** 2012; ***J Proteome Res*** 2012; ***J Bacteriol*** 2012; ***Inf Immun*** 2012). Dette er studert med bakterier som modellsystemer, imidlertid har slike modifikasjoner stor betydning for hvordan hjernens celler henger sammen og ikke faller fra hverandre. Disse og en rekke andre funn ved CMBN i 2012 er nyskapende og interaktiv frontlinjeforskning, med betydelig potensial for utvikling av tidlig diagnostikk, forebygging og behandling.

CMBN-forskere har i stor grad bidratt til det vitenskapelige innholdet i MindGap-utstillingen på Teknisk Museum, som trakk et tallrikt publikum i alle aldre 2011-2012. Utstillingens kunsteriske leder var Robert Wilson, USA. For å bidra ytterligere til utstillingen og dens profil mot publikum, organiserte Hjernerådet (som CMBN var med på å stifte) og CMBN-forskere "Hjernelørdag". Der ga CMBN-forskere og stipendiater populærvitenskapelige foredrag og bidro med disseksjon av grisehjerner slik at folk virkelig kunne se og føle hjernens struktur. En annen satsning fra CMBN i 2012 var organisering av den internasjonale konferansen Genome Dynamics in Neuroscience (GDN4; www.GDN4.com), som trakk anerkjente forelesere og deltakere fra mange deler av verden. Det lages et hefte i tidsskriftet Mechanisms of Ageing and Development med artikler fra møtet, noe som også er et nytt læringsverktøy for et fagfelt i rask utvikling. CMBN har også organisert en rekke andre internasjonale møter i 2012 og har fortsatt tradisjonen med å arrangere Nansen Neuroscience Lectures 10. oktober, i samarbeid med Nansen Neuroscience Network og Det Norske Videnskaps-Akademi.

Vår ambisjon er å inspirere kreativiteten, kompetansen og produktiviteten til våre flotte forskere og studenter ved CMBN, for å sikre og forsterke deres suksess. På dette stadiet i CMBN-prosjektet er en vellykket innfasingsstrategi på agendaen. I denne prosessen er vi spesielt takknemlige overfor våre vertsinstitusjoner, Universitetet i Oslo og Oslo universitetssykehus, for deres omhyggelige bestrebelser for å ivareta verdien av vårt senter. Sammen har vi utviklet en ny innfasingsstrategi, som bygger på SFFFIII-søknader som utgikk fra CMBN. Derved kan oppdagelsene og kompetansen ved CMBN ivaretas og bli fullt integrert i et langtidsperspektiv, med utbyttet og den faglige arven om bord.

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