CENTRE FOR
MOLECULAR BIOLOGY
AND NEUROSCIENCE

Centre for Molecular Biology and Neuroscience

Centre of excellence

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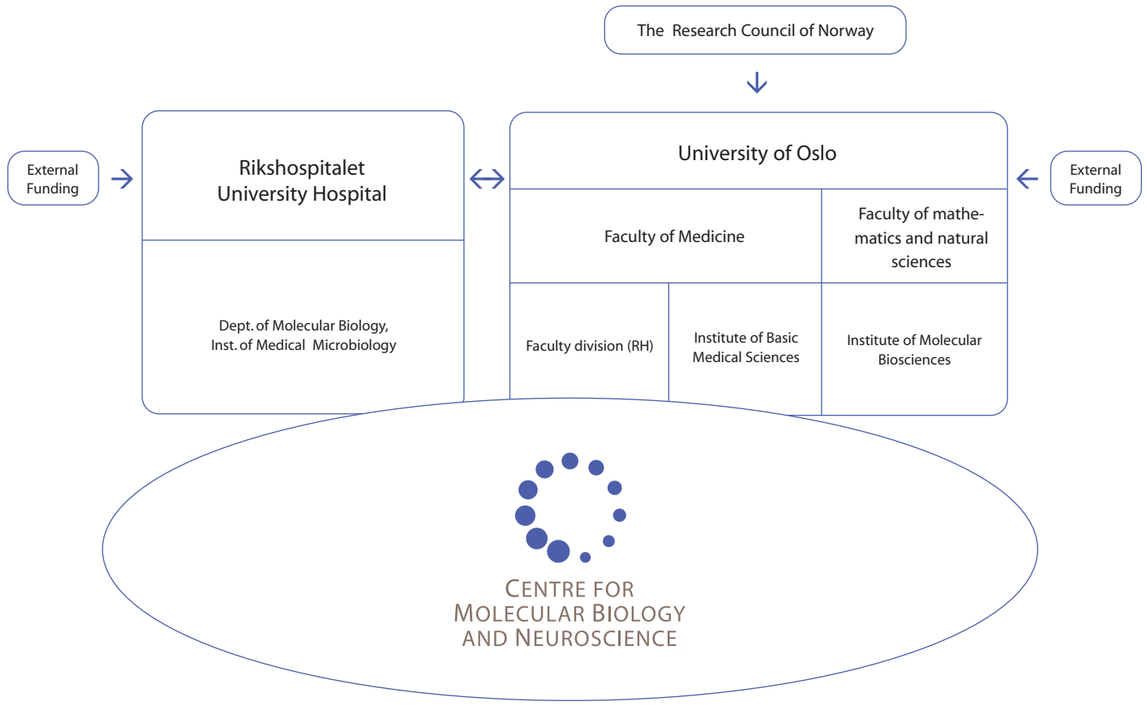
Norwegian Centre of Excellence
UNIVERSITY OF OSLO
Rikshospitalet University Hospital

CMBN

ABOUT

The Centre for Molecular Biology and Neuroscience (CMBN) at the University of Oslo (UiO) and Rikshospitalet University Hospital (RH) is a Norwegian Centre of Excellence, appointed by the Research Council of Norway. The Centre`s main activities are located at Gaustad, in two adjacent buildings belonging to the University and Rikshospitalet, respectively.



OBJECTIVES

The Centre shall take on a leading role in elucidating the role of DNA repair and genome maintenance mechanisms in preventing neurological disease and brain ageing. The Centre will develop and apply stem cell technology and targeted repair to broaden the range of therapeutic strategies in neurological disease. The centre will also investigate the processes that are upstream of DNA damage in nerve cells and will explore the excitotoxic hypothesis which holds that DNA damage may be caused by overstimulation of glutamate receptors and subsequent formation of oxygen radicals. Progress in this field will require a better understanding of the function and molecular organization of the glutamate synapse.

THE BOARD

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

- Prof. Ole M. Sejersted, University of Oslo (Chairman)
- Director Prof. Olli A. Jänne, Biomedicum Helsinki, Finland
- Director Per Morten Vigtel, Norsk Investorforum
- Senior Adviser Inger Nina Farstad, Rikshospitalet University Hospital
- Head of Department Peter Gaustad, Rikshospitalet University Hospital
- Professor Borghild Roald, University of Oslo

RESEARCH

The Centre consists of 11 research groups at the University of Oslo (UiO) and Rikshospitalet University Hospital (RH). In total, more than 100 people are involved in the research at CMBN. The Group leaders are:

RESEARCH GROUPS

- Ole Petter Ottersen, UiO (Director)
- Erling Seeberg, RH/UiO (Ass. Director)
- Jan G. Bjaalie, UiO
- Nils Christian Danbolt, UiO
- Arne Klungland, RH
- Michael Koomey, UiO
- Stefan Krauss, RH/UiO
- Torbjørn Rognes, RH
- Johan Storm, UiO
- Jon Storm-Mathisen, UiO
- Tone Tønjum, RH/UiO

MANAGEMENT AND ORGANIZATION

The Centre is led by Ole Petter Ottersen (Director) and Erling Seeberg (Ass. Director). Peder Heyerdahl Utne is the administrative leader of the Centre. The Centre has a Steering Group that meets on a regular basis and that consists of the eleven group leaders of the consortium.

BUDGET AND FUNDING

CMBN's annual budget is almost NOK 100 mill. Among the organizations that support the Centre and its research groups are the following:

- The Research Council of Norway
  - Norwegian Centres of Excellence
  - Medicine and Health (MH) Group
  - Functional Genomics in Norway (FUGE)
  - Toppforskningsprogrammet
- University of Oslo
- Rikshospitalet University Hospital
- Norwegian Cancer Society
- European Union
- Welcome Trust

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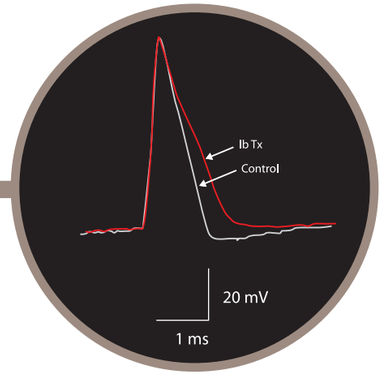
LABORATORY OF CELLULAR NEUROPHYSIOLOGY AND ION CHANNEL FUNCTION

ABOUT

Our group is interested in brain function, from molecules to behavior. We study fundamental principles and mechanisms of neuronal signalling in the mammalian brain, and the roles of ion channels in behavior, brain function, and disease. We focus on the functions of ion channels, in particular K^+ channels, in central neurons and circuits, mainly in the hippocampus and cerebral cortex. Methods: Electrophysiological and optical recordings in brain slices and in vivo, molecular genetic and pharmacological manipulations, computational modelling, and behavioral tests.



Action potentials in brain neuron (hippocampal pyramidal cell) before and after blockade of BK- type (potassium) channels.

CHALLENGES

- To determine the functional roles and interplay of multiple signalling mechanisms and ion channel types within different neuronal compartments and within the entire neurone.
- To elucidate functional roles of specific neuronal populations, signalling mechanisms and ion channel types, in active neuronal networks, and in the brain of behaving animals.
- To elucidate the roles of neuronal signalling mechanisms in ageing and neurological disease, including neurodegenerative and ischemic disorders, epilepsy, and memory disorders.

PROJECTS

- The roles of M-/KCMQ- and h/HCN-type K^+ channels in neuronal signalling, brain oscillations, synaptic plasticity, cognitive functions and epilepsy.
- The roles of Ca^{2+}-activated K^+ channels (BK and SK channels) in neuronal signalling, synaptic plasticity, cognitive functions, motor control, epilepsy and neuroprotection.
- The roles of voltage-gated ion channels in neuronal signalling, synaptic plasticity, learning and memory.
- Changes in neuronal signalling during ontogenetic development and ageing.

Recent achievements: Discovered and characterized: that BK-type K^+ channels are essential for cerebellar learning and motor control (submitted 2004), that M-type K^+ channels are essential for spatial learning and prevention of epilepsy (submitted 2004), the role of postsynaptic voltage-gated K^+ channels in regulation of synaptic plasticity (LTP) and integration (Proc Natl Acad Sci USA 99:10144, 2002); the ionic mechanisms of intrinsic theta resonance in hippocampal neurons (J Physiol 545:783, 2002); the cellular and subcellular distributions and pre- and postsynaptic functions of BK- and SK-type Ca^{2+}-activated K^+ channels (J Neurosci 21:9585, 2001; J Neurosci 22:9698, 2002; J Physiol 536: 809, 2001).

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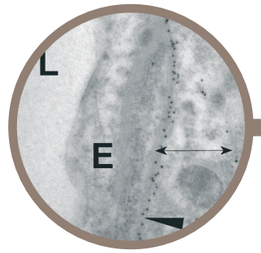
LABORATORY FOR MOLECULAR NEUROSCIENCE

ABOUT

The Laboratory for Molecular Neuroscience investigates molecular mechanisms involved in the development of acute and chronic neurodegenerative disease, with a focus on the role of glutamate excitotoxicity. It aims at unravelling the molecular basis for cell death and edema development in stroke, and explores the pathophysiology of Alzheimer's disease and temporal lobe epilepsy. One of the long term goals is to identify new molecular targets for neuroprotective strategies in stroke and other conditions involving glutamate excitotoxicity.



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

CHALLENGES

Neurology continues to lag behind other disciplines when it comes to the range and efficacy of therapeutic strategies. In particular, common neurological conditions such as stroke, Alzheimer's disease, and other acute or chronic neurodegenerative diseases call for new therapeutic strategies. Several of these conditions are particularly prevalent among the elderly and will constitute a growing health concern as the population ages. The challenge is to identify new principles of treatment for these diseases.

PROJECTS

- Assessing the role of water channel molecules (aquaporins) in the development of brain edema and in the regulation of ion homeostasis in brain extracellular fluid.
- Exploration of the composition and function of the protein complexes that interact with glutamate receptors and that mediate downstream signalling from these.
- Unravelling the synaptic expression of kainate, NMDA, and AMPA receptors and the mechanisms responsible for their turnover.
- Identification of mechanisms underlying loss of glutamate homeostasis in temporal lobe epilepsy.
- Exploration of mechanisms involved in the formation of beta-amyloid in aging and Alzheimer's disease

Recent achievements: Resolving modes of NMDA and AMPA receptor expression in hippocampal spine synapses (Nature Neuroscience 2:618-624, 1999). Identification of principles underlying expression and regulation of the water channel aquaporin-4 in the CNS (J Neurosci 17:171-80, 1997; J Neurosci 21:3045-51, 2001; PNAS 98:14108-13, 2001). Showing that removal of perivascular aquaporin-4 protects against development of postischemic edema and delays K^+ clearance from the extracellular space (PNAS 100:2106-11, 2003; PNAS, 100:13615-20, 2003, Nature Reviews Neuroscience, 4:991-1001, 2003). Identification of neuronal plasma membrane microdomains that colocalize beta-amyloid and presenilin (Neuroscience, 120:291-300, 2003). Demonstrating that loss of glutamine synthetase may contribute to increased glutamate levels and seizure precipitation in patients with temporal lobe epilepsy (Lancet, 2004 Jan 3;363(9402):28-37).

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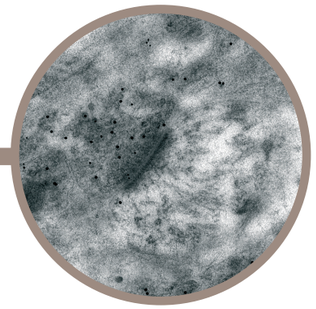
THE SYNAPTIC NEUROCHEMISTRY LABORATORY

RECYCLING AND PACKAGING OF TRANSMITTER AMINO ACIDS

ABOUT Main interests are the mechanisms underlying synaptic transmission: localization, transport, synthesis, release and breakdown of neurotransmitters (glutamate, aspartate, GABA, glycine, monoamines, acetylcholine). These mechanisms are studied in normal and pathological conditions, and during ontogenetic development and ageing.



A rare hippocampal nerve ending with two different glutamate transprorters VGLUT1 (big dots) and VGLUT2 (small dots) in its synaptic vesicles (V Gundersen)

CHALLENGES Recent research by our group has opened possibilities for studying in depth aspects of nervous system functions in health and disease. An important aspect is how nerve endings provide glutamate for synaptic release and how they recover released glutamate for reuse. Thus the molecular identification and characterization of glutamine transporters, SN (Cell 1999, EMBO J 2001, Eur J Neurosci 2002, Glia 2003) and SA/SAT (PNAS 2000, J Neurosci 2002, J Cell Biol 2002), and the ultrastructural localization of monocarboxylate transporters (Cereb Cortex 2004) provide new approaches to understanding synaptic function. The identification of proteins, VGLUT1-3 (Neuron 2001, PNAS 2002), that pump glutamate into synaptic vesicles allows the packaging of the transmitter to be characterised and modified (Science 2004). The observation that even astrocytes (Nature Neurosci 2004) and neuroendocrine cells (J Cell Sci 2004) can release glutamate in a way resembling synaptic release, together with findings that glutamate and other neuroactive substances can be co-released from nerve endings (Eur J Neurosci 2003, Molec Neurosci 2004), suggests novel ways of intercellular communication.

PROJECTS

- The role of glutamine, versus other metabolic precursors of glutamate, for keeping up synaptic release. Transporters and metabolising enzymes are located immunocytochemically and their functional roles studied in oocytes and cultured cells by artificial expression, and in animals with modified or blocked expression of the specific genes.
- Interplay of glutamate with e.g. aspartate, GABA or glycine at brain synapses and endocrine cells. Localisation of the amino acids and their transporters, receptors and enzymes in normal and experimentally modified animals, including animal models of neurological disease (e.g. epilepsy).
- Synaptic changes during ontogenetic development and in animals with deficient DNA repair.

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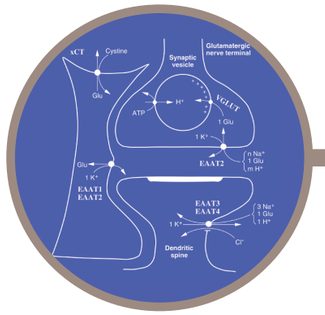
THE NEUROTRANSPORTER GROUP

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



The distribution of glutamate transporter proteins

CHALLENGES The human genome contains about 500 different transporter protein genes. Many of the encoded transporters, including those for glutamate, are subject to sophisticated dynamic regulation, and are also ion channels in addition to being transporters. Thus, the transporters appear to have more refined functions than just being pumps, but these functions are poorly understood. The overall aim of the Group is to determine the roles of the individual transporter subtypes in order to better understand normal physiology and disease, and to uncover new therapeutic opportunities. Disturbed control of extracellular glutamate appears to be an important factor, directly or indirectly, in all neurological disorders as well as in drug abuse and major psychiatric disorders (e.g. schizophrenia), as a consequence of the abundance of glutamate, the ubiquitous presence of glutamate receptors, and the interplay between glutamate, oxidation and energy metabolism (for review see: Danbolt, 2001: Prog. Neurobiol).

PROJECTS

- Production of suitable tools (including antibodies) and model systems (including gene modified animals)
- Determination of transporter distributions and densities around select synapses in normal adult brains and how these parameters change during development, ageing, drug use and disease
- Computer modelling of transmitter release, diffusion, removal and receptor activation
- Transporter protein purification, reconstitution and crystallisation

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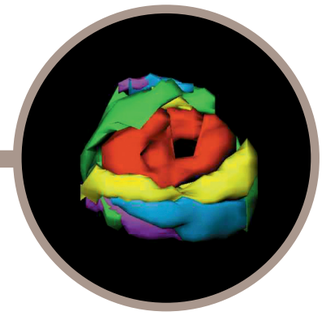
NeSys – NEURAL SYSTEMS AND GRAPHICS COMPUTING LABORATORY

ABOUT

NeSys is a computational neuroanatomy and neuroinformatics laboratory. The research of the group focuses on 1) the development of new and powerful methods for computerized data acquisition, 3-D reconstruction, visualization and quantitative analyses of features in brain tissues, 2) data management and construction of 3-D brain atlases of experimental data, and 3) investigations on organization and re-organization of brain systems architecture in rat and mouse models.

CHALLENGES

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



3-D mapping of body parts in a small part of the brain: basis for studying re-organization

PROJECTS

- Neuroscience image databases. We develop and implement databases and tools in collaboration with the Central University Computing Services at the University of Oslo, Centre Guest Professor Shankar Subramaniam at the San Diego Supercomputing Center, and multiple contributing laboratories in Europe and the USA.
- Digital atlasing; localization in the brain. We develop and use digital atlases for efficiently assigning locations to neuroscience data.
- Brain map transformations. Our research includes studies of brain map transformations and systems level organization, with use of digital atlases and databases. We employ mouse models for studying changes in architecture and design of circuits and regions in the brain, following external and genetic manipulations.

Key achievements: Development of neuroinformatics tools for advanced visualization and mathematical analysis of architecture at multiple levels (J Neurosci. 18:10603-18, 1998). Implementation of relational database and brain atlas systems allowing continued and dynamic use of published data (Nature Rev Neurosci. 3:322-5, 2002) and contributions to science policy developments in this field (Neuroinformatics 1:149-166, 2003). Principles of map transformations in major circuits of the brain (J Comp Neurol. 422:246-266, 2000; J Neurosci. 20:8474-8484, 2000).

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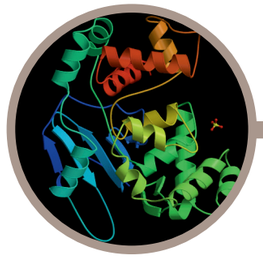
THE BIOINFORMATICS GROUP

ABOUT

The Bioinformatics group is using computers to analyse genome sequences to find new genes and determine their function. Advanced statistical and computational tools are used and developed to find patterns and particular sequences that indicate the presence of genes and regulatory elements. In order to identify new relationships between genes, improved methods are being developed to compare sequences and to search sequences databases. The group is also creating databases with information about genes of particular interest, e.g. genes involved in DNA repair. At present (2004) the group consists of seven people.

CHALLENGES

Sequencing centres around the world have now determined the complete genome sequences of more than 150 organisms. These efforts have resulted in huge amounts of sequence data that are still growing rapidly. The challenges are to find out in detail what genes and other signals these sequences consist of, and what the form and function of the gene products are. Computational analyses of the sequences can often answer many of these questions, and is a great help for later experimental biochemical work. The group is therefore working closely with other groups that study genes using advanced molecular biology methods.



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

PROJECTS

- Sequence similarity searches: Novel tools (e.g. ParAlign) for rapid and sensitive sequence database similarity searches have been developed and are now available at www.paralign.org on the Internet. Parallelisation and advanced hardware features are exploited to get the highest performance.
- DNA repair genes: General sequence analysis and computational identification of new DNA repair genes are important topics where the group collaborates closely with other groups. Therefore, we are creating a web portal with an underlying database containing information on DNA repair genes.
- Non-coding RNA genes: The group is working to develop methods to identify new members of an interesting class of genes that does not encode proteins, but stable and functional non-coding RNA genes (ncRNA).
- Protein structure: A protein 3D structure visualisation and modelling lab is being established. New strategies for classifying protein structure topologies are being investigated.
- Statistical sequence analysis: Analysis of the abundance and distribution of over- and under-represented oligonucleotides in genomic sequences has led to interesting findings.

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

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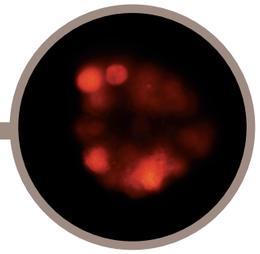
GENOMIC (IN)STABILITY GROUP

ABOUT

Repair of DNA damage is essential for protection against cancer and other age related diseases. Such diseases are believed to be initiated by mutations and rearrangements of the DNA sequence. DNA damage generated by ionising radiation, simple alkylating agents or endogenously hydrolytic and oxidative processes is corrected by the base excision repair (BER) pathway.



Induced oxidative stress leads to apoptosis in Fen1 mutant blastocysts (MCB, 2003)

CHALLENGES

We use standard molecular biology strategies, including the construction of cells and animals lacking specific DNA repair functions, to Identify and characterize gene-functions for repair of DNA damage. Such models aim to elucidate the contribution of single genes for protection against mutations, genomic instability, ageing and ageing related diseases such as cancer. Several collaborations, internationally and within the Centre for Molecular Biology and Neuroscience, have been initiated.

PROJECTS

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

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

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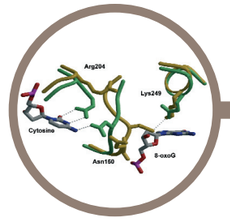
LABORATORY FOR MOLECULAR BIOLOGY

ABOUT

The Laboratory for Molecular Biology investigates basic biological processes associated with cellular responses to DNA damage including DNA repair pathways and mechanism for tolerance, scavenging and adaptation. Focus has been on the repair of endogenous DNA damage and mechanisms for removal of base damage to DNA. At the cellular and organismal level, the aim is to understand mechanisms for genome maintenance in mammalian as well as microbial cells and to develop new interventions for preventing cancer and neurological disease associated with genome instability caused by DNA damage.



Protein conformational changes associated with DNA damage recognition (hOGG1, Yellow: native; green: bound to DNA)

CHALLENGES

Cellular genomes are continuously challenged by physical, chemical and biological agents that introduce changes of the chemical structure of the DNA. Intracellular reactive metabolites such as reactive oxygen species and alkylating compounds are important inducers of such changes. Nevertheless, mutation frequencies are low because of very efficient pathways for DNA repair and DNA recombination, which remove DNA damage and conserve at least one functional copy of the genome. Nevertheless, in humans, DNA damage will induce genome instability that is associated with disease and degenerative disorders. Challenges are to understand the mechanisms for cellular protection against DNA damage and its role in cancer, ageing and neurological disease.

PROJECTS

- Alkylation and oxidative DNA damage and repair - role in ageing, cancer and neurological disease
- Functional genomics of DNA repair
- Model studies of DNA repair and ageing in yeast
- RNA genes in biological responses to DNA damage
- Mechanisms of DNA repair and genome maintenance in microbial cells and animal viruses
- Genome stability and maintenance in stem cells
- The WRN premature ageing syndrome and role in DNA recombination

Key achievements: Basic biology of nucleotide excision repair (Nature 263:524-6, 1976; PNAS 75:2569-73,1978; PNAS 79:988-92,1982; PNAS 87:191-4,1990; EMBO J. 3:757-60, 1994), genetics and mechanisms for repair of alkylation damage to DNA (JMB 140:101-27,1980; Nature 296:775-7,1982; EMBO J 9:4563-8,1990; EMBO J 17:363-7,1998; Nature 419:178-82,2002; Nature 421:859-63,2003), identification, cloning and characterization of genes for repair of oxidative DNA damage in eukaryotes (PNAS 93:10735-40,1996; EMBO J 16:6314-22,1997; MCB 19:3779-87,1999; NAR 30:4926-36,2002). Significant contributions have also been made in the fields of brain glutamate transport (Nature 360:464-7,1992, Eur. J. Nurosci., 6:936-42,1994), haematopoiesis (Blood 91:4127-35,1998), and bioinformatics (Bioinformatics 16:699-706,2000)

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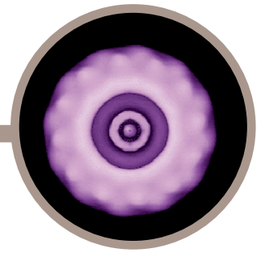
GENOME DYNAMICS AND MICROBIAL PATHOGENESIS

ABOUT

The stability of microbial genomes and gene pools is constantly challenged by horisontal gene transfer and recombination, as well as DNA damage. Mechanisms for rapid genome variation, adaptation and maintenance are a necessity to ensure microbial fitness and survival in rapidly changing environments. Understanding microbial pathogenesis, horisontal gene transfer and DNA repair mechanisms requires an interdisciplinary approach of molecular biology, genomics and bacterial physiology. Studies on transformation and components providing genome maintenance in genetic model bacteria are most important for understanding the balance between cellular fitness for survival and disease development (Trends Microbiol 2001, 2004). At present the group addressing these challenges in molecular and cellular biology and medicine includes eleven people and has strong international networks.



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

CHALLENGES

To dissect how genome dynamics affect DNA sequence variability and conservation and thereby influence microbial fitness for survival and pathogenesis. Our analysis of surface structures and genome maintenance components will provide new insight into bacterial fitness and virulence. In the long run this information will enable us to develop new strategies for prevention and treatment of disease which also has relevance for eukaryotic systems.

PROJECTS

- Meningococcal pilus biogenesis and DNA uptake: Neisseria meningitidis is the causative agent of meningitis. Pili are the primary virulence factor of this exclusively human pathogen. The transport of these macromolecular structures across membranes is performed by a complex machinery. We are characterising the structure-function relationship and interactions of components involved in the membrane transport of pili and DNA (Mol Microbiol 1998).
- Genomics in the search for novel signature DNA sequences: We are using our combined expertise on evolutionary phylogeny, prokaryote cell physiology and comparative genomics to identify new signature sequences. We are currently defining new tools to target novel DNA binding proteins (Nucl Acids Res 2004).
- Intracellular survival of Mycobacterium tuberculosis: M. tuberculosis is the cause of tuberculosis. Inside the macrophage phagolysozome, M. tuberculosis faces unusually harsh challenges. We are studying the mechanisms for genome maintenance and thereby fitness for survival in the world's biggest bacterial killer.

Recent achievements: Bias of DNA uptake sequences (NAR 2004), secretin PilQ structure (JMB 2004).

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BACTERIAL PATHOGENESIS

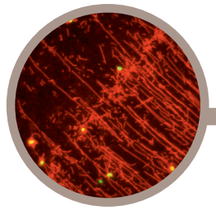
MOLECULAR AND CELL BIOLOGY

ABOUT

The main interests of the group lie in studies of how bacterial pathogens cause disease in man. Our research is focused particularly on bacterial surface organelles termed Type IV pili (Tfp) or fimbriae. Tfp expressing bacterial pathogens are responsible for an extensive amount of morbidity and mortality worldwide. In addition, Tfp are associated with horizontal gene transfer and therefore contribute to the evolution of pathogenic and antibiotic reistant microbes. Based on both its relevance to other human diseases and its amenability to in vitro manipulation and analysis, we have chosen the human pathogen Neisseria gonorrhoeae, the agent of gonorrhea, as a model system.

CHALLENGES

We use standard molecular biology strategies, together with classical genetic, genomic and proteomic approaches to elucidate the mechanisms of Tfp biogenesis and the structure/function relationships accounting for Tfp associated phenotypes. The intention is that by understanding the molecular basis for these processes, it will be possible to design rational approaches to preventing and controlling disease. Several international collaborations are ongoing.



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

PROJECTS

- Tfp biogenesis and dynamics of expression: Our studies have been instrumental in defining a unique and ubiquitous pathway by which bacterial surface organelles are assembled.
- Tfp structure and components: A large array of mutants which have been used to demonstrate the association of minor components critical to Tfp function. In addition, post-translational modifications of the pilin subunit have been identified and characterized. Future aims are to determine the structure of the Tfp filament at atomic resolution.
- Function of Tfp in human cell adherence: In conjunction with the structural studies, Tfp associated components required for human cell adherence (and thus disease) have been identified and are being characterized.
- Function of Tfp in natural genetic transformation: Tfp, together with components related to Tfp expression, are involved in virtually all natural transformation systems in bacteria. Our work on the gonococcal system has revealed that an intact Tfp biogenesis machinery is essential to both the DNA binding and DNA uptake steps of transformation. Molecules dispensable for Tfp expression have also been found to act at these steps. Studies of the interaction of the Tfp biogenesis components and these ancillary factors are ongoing.

Recent achievements: dynamics of pilus expression (PNAS 1998); essential genes in N. gonorrhoeae (EMBO J 2000); a unique pilus biogenesis pathway (EMBO J 2000) and identification of a novel pilus associated adherence protein (PNAS 2001).

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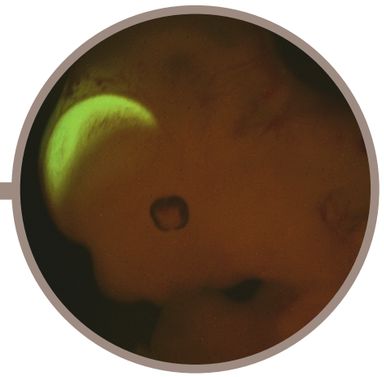
FOREBRAIN DEVELOPMENT AND NEURAL STEM CELLS

ABOUT

The developmental biology laboratory investigates the signalling mechanisms that control fate specification and proliferation in the mouse cortex.



The D6 enhancer allows selective genetic manipulation in the mouse cortex

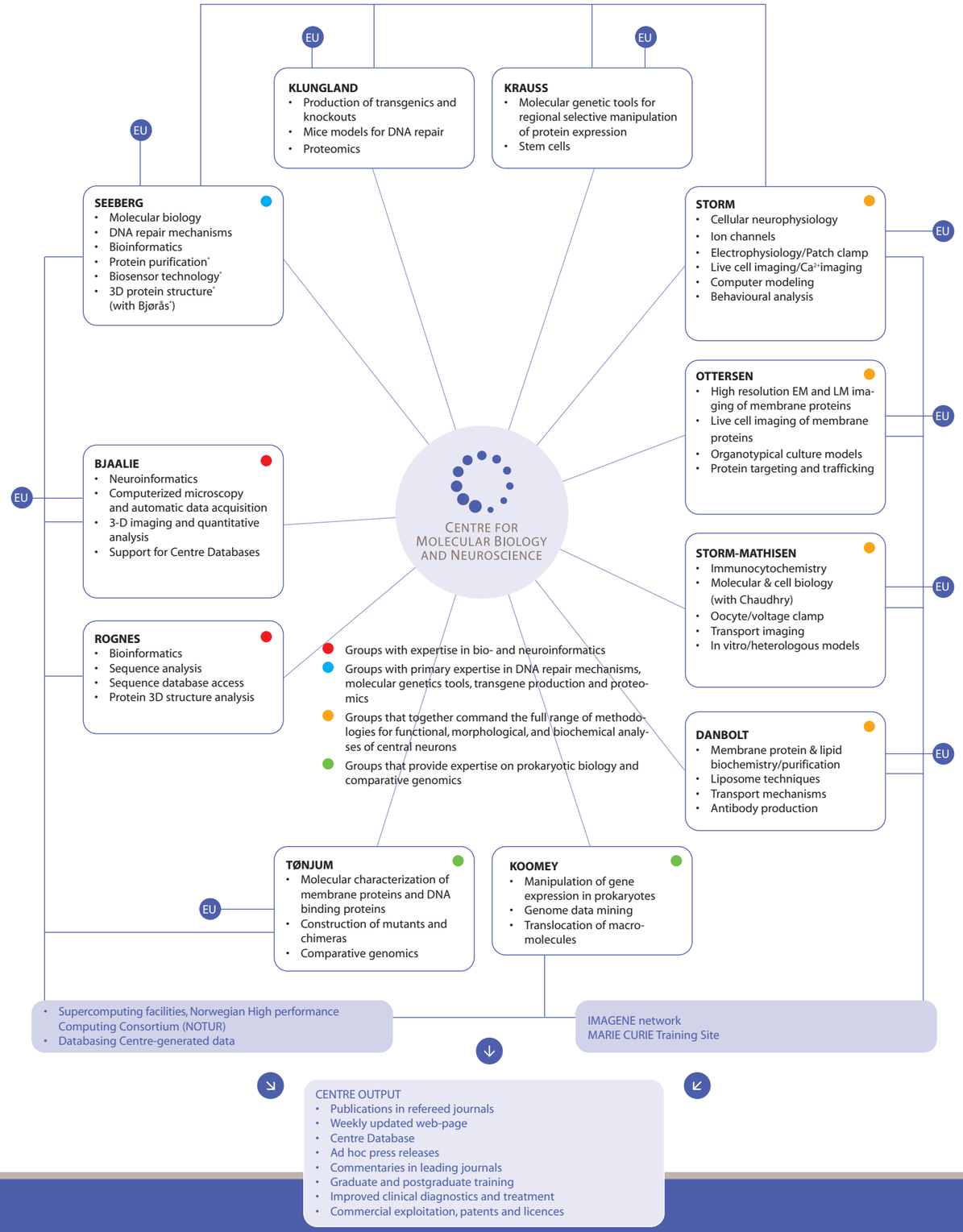
CHALLENGES

The aim of the ongoing study is to deepen our understanding of signalling pathways that are involved in cortical development, sub-specification of cortical areas, proliferation and communication between supporting cells. Disease models will be established that shall cast light on the function of morphogenetic signals in ageing and dementia. This knowledge should help to develop new strategies for prevention and treatment of disease, either by identifying drug targets, or by developing cell based delivery of therapeutic signals.

PROJECTS

- Understanding cortical development and evolution through cell culture and transgenic model systems.
- Study interaction and convergence of cortical signalling in animal and cell culture systems
- wnt signalling in cortical maturation and ageing

Key achievements: Discovery of key signal Shh (Cell 1993). Mutant for manipulation of anterior inductive zone AER (Nature Genetics 1998). Cortex specific manipulation of Wnt signalling (Neuroscience 2003).



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