The 2nd NO-Age Symposium on ‘Genomic instability in human brain’

on 12th June 2019, University of Oslo

Organizers
Evandro F. Fang, Hilde Nilsen
Linda Bergersen, Jon Storm-Mathisen

Venue: NN5, Akershus University Hospital, 1478 Lørenskog, Norway

Programme (12th June 2019)

Venue:
NN5 (The 5th floor audotrium) in the '**Nye nord Nordbyhagen**' building, Akershus University Hospital, 1478 Lørenskog, Norway).

Morning Session: Genomic instability in disease and ageing

Moderator: Hilde Nilsen

08:00-08:10: Welcome speech Dr. Helge Røsjø (Research Director, Akershus University Hospital)
08:10-08:20: Opening Evandro and Hilde Nilsen
08:20-09:00: Vilhelm A. Bohr (NIA/USA, Copenhagen) **Keynote speaker**
09:00-09:30: Peter McHugh (Oxford)
09:30-10:00: Tinna Stevnsner (Aarhus)
10:00-10:20: Break and networking
10:20-10:50: Magnar Bjoras (UiO and NTNU)
10:50-11:20: Hilde L. Nilsen (Ahus and UiO)
11:20-11:50: Arne Klungland (UiO)
11:50-12:10: Minoru Takata (Kyoto, Japan)
12:10-12:30: Jinsan ZHANG (WZMU, China)
12:30-12:35: Jian XIAO (WZMU, China)

12:35-13:30: Lunch

Session theme: Advances in healthy brain ageing

Moderator: Evandro Fang

13:30-14:00: Tormod Fladby (Ahus, UiO)
14:00-14:30: Willam McEwan (Cambridge)
14:30-15:00: Linda Bergersen (UiO and Copenhagen)
15:00-15:30: Break and networking
15:30-16:00: Evandro F. Fang (Ahus, UiO)
16:00-16:30: Hansang Cho (University of North Carolina at Charlotte, USA)
16:30-17:00: Leiv Otto Watne (UiO)
17:00-17:30: Jens Pahnke (UiO)

18:30-21:30: Dinner (Solsiden Restaurant, Akershusstranda 13, skur 34, 0150 Oslo +47 22 33 36 30)

All welcome. Please have your free register here https://noage100.com/contact2/

The Initiative Committee of NO-Age

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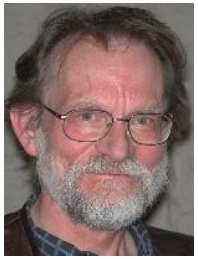

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Stuff

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Financial Sponsors

Name: Vilhelm Bohr
Institute: National Institute on Aging, NIH
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Keynote Speaker: Vilhelm Bohr

Title: DNA damage leads to mitochondrial dysfunction and neurodegeneration

Abstract: We find that some DNA repair defective diseases with severe neurodegeneration have mitochondrial dysfunction. Our studies involve cell lines, the worm (*C. elegans*), and mouse models and include the premature aging syndromes Xeroderma pigmentosum group A, Cockayne syndrome, Ataxia telangiectasia and Werner syndrome. We find a pattern of hyper-parylation, deficiency in the NAD^+ and sirtuin signaling and mitochondrial stress. We are pursuing mechanistic studies of this signaling and interventions at different steps to improve mitochondrial health and the neurodegeneration. I will discuss interventional studies in these diseases models including a new Alzheimer mouse model using NAD supplementation. NAD supplementation stimulates mitochondrial functions including mitophagy and stimulates DNA repair pathways. Based on human postmortem material and IPSC cells we identify mitophagy defects as a prominent feature in Alzheimer's disease (AD). Using *C. elegans* AD models we screened for mitophagy stimulators and identified compounds that subsequentially also show major improvement of AD features in mouse models.

Biography:

Dr. Bohr received his M.D. in 1978, Ph.D. in 1987, and D.Sc. in 1987 from the University of Copenhagen, Denmark. After training in neurology and infectious diseases at the University Hospital in Copenhagen, Dr. Bohr did a postdoctoral fellowship with Dr. Hans Klenow at the University of Copenhagen, Denmark. He then worked with Dr. Philip Hanawalt at Stanford University as a research scholar from 1982-1986. In 1986 he was appointed to the National Cancer Institute (NCI) as an investigator, becoming a tenured Senior Investigator in 1988. Dr. Bohr developed a research section in DNA repair at the NCI. In 1992 he moved to the NIA to become Chief of the Laboratory of Molecular Genetics. His main contributions have been in the area of DNA repair. He has worked on many aspects of DNA damage and its processing in mammalian cells. He developed a widely used method for the analysis of DNA repair in individual genes and found that active genes are preferentially repaired. This observation was a major advance in the clarification of the tight interaction between DNA repair and transcription, a process termed transcription-coupled repair. In recent years numerous papers from his laboratory have focused on mechanisms of DNA damage processing, particularly on nucleotide excision repair and transcription coupling. A main interest now is to elucidate how these processes change in relation to aging.

Name: Peter J. McHugh
Institute: **University of Oxford**
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Speaker: **Peter McHugh**
Title: The mechanisms of XPF-dependent DNA crosslink repair: a pathway required to suppress accelerated ageing?

Abstract:
The XPF and ERCC1 proteins form a heterodimeric endonuclease that plays a critical role in Nucleotide Excision Repair (NER) and also in the replication-coupled repair of DNA interstrand crosslinks (ICLs). Mutations in the XPF or ERCC1 genes cause a remarkable array of rare inherited human disorders, several associated with features of premature ageing and neurodegeneration, including Xeroderma pigmentosum, Cockayne syndrome, Fanconi anemia, and cerebro-oculo-facio-skeletal syndrome. A key, initiating event in ICL repair is incision of crosslink-arrested replication fork structures, which requires the XPF-ERCC1. Despite this, structures that model replication forks stalled by ICLs are very poor substrates for XPF-ERCC1 *in vitro*, indicating that additional, unidentified factors are required to target and activate this key nuclease during repair

Our recent work has demonstrated that during replication-coupled ICL repair, arrested replication fork intermediates can be processed through the dramatic stimulation of XPF-ERCC1 by both RPA and repair nuclease platform protein SLX4 ^{FANCQ}, and this is likely to be critical for the repair of ICL damaged replication forks *in vivo*. Here, I will describe our progress towards the full biochemical reconstitution of this critical DNA repair pathway.

Biography: Peter McHugh is Professor of Molecular Oncology and Director of the Oncology Laboratories at the MRC-Weatherall Institute of Molecular Medicine. Following a a D.Phil in Biochemistry at the University of Oxford and a period of post-doctoral research at University College London, he was awarded a Royal Society University Research Fellowship in 2001. In 2003 he joined the Oncology Laboratories at the MRC Weatherall Institute of Molecular Medicine, where he heads the DNA Damage and Repair research group.

Name: Tinna Stevnsner
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Speaker: Tinna Stevnsner
Title: Mitochondrial metabolism and DNA repair in maintenance of cognitive capacity at very old age

A growing proportion of the population is surviving to a very high age and cognitive changes as a normal process of aging is well documented. However, there are substantial individual differences in the rate and magnitude of age-associated cognitive decline. DNA repair capacity, optimal mitochondrial function and a sufficient level of NAD+/NADH are some of the factors, which seem to be essential for optimal brain function. In order to get insight into the molecular mechanisms involved in maintenance of cognitive capacity at very old age we are investigating potential associations between cognitive capacity in a cohort of Danish centenarians and the above-mentioned biomarkers in the blood. We find a positive correlation between NAD+/NADH levels in the centenarians' plasma and their cognitive capacity. Our data reveal a negative correlation between cognitive capacity and the level of carbonylated proteins and APE1/Ref1 protein in plasma, respectively. When studying peripheral blood lymphocytes isolated from the blood samples of the centenarians we find a positive correlation between cognitive capacity and APE1 endonuclease amount and activity. Finally, mitochondrial respiratory measures were found to be significantly increased in males with low cognitive capacity. The observed associations contribute to an expanded insight into the potential role of a range of molecular factors involved in maintenance of cognitive capacity at old age and also point to metabolic pathways of particular importance.

Biography:
Dr. Tinna Stevnsner is an associate professor and principal investigator in a research laboratory at Department of Molecular Biology and Genetics. Her research focuses on the role of nuclear and mitochondrial genome maintenance in aging. Recently, much of her research has been directed towards the elucidation of molecular pathways involved in maintenance of cognitive capacity at old age.

Tinna did her PhD work in the laboratory of Vilhelm A. Bohr at National Cancer Institute, NIH, USA, where she investigated aspects of gene specific repair in mammalian cells. Afterwards, she worked for four years as a post doc at Dep. of Environmental and Occupational Health at Aarhus University, Denmark, where she studied DNA repair capacities in cultured lymphoblastoid cells and PBMCs from patients suffering from premature aging syndromes and bladder cancer patients, respctively. Next, she moved on to her current place of work. In 2014 she visited the laboratory of prof. Carl Cotman at University of California, Irvine, USA, for six months. There, she investigated the age-associated expression of base excision repair (BER) proteins in different regions of the human brain and studied the potential role of Brain-derived neurotrophic factor (BDNF) in the regulation of BER in neurons.

Name: Magnar Bjørås
Institute: Norwegian University of Science and Technology (NTNU)
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Speaker: Magnar Bjørås

Title: Diverse functions of DNA glycosylases processing oxidative DNA damage in brain

Abstract:
DNA glycosylases initiate base excision repair (BER) by eliminating modified bases that can cause cytotoxicity, mutations and ultimately cancer. Though Neil DNA glycosylases remove a broad spectrum of presumably mutagenic and hence cancer-promoting oxidative DNA base lesions, surprisingly we found that *none of the Neil deficient mouse strains are prone to develop cancer, including the Neil123 triple deficient mice*. Furthermore, none of the Neil-deficient mouse strains display a higher spontaneous mutation frequency than wild-type mice or accumulate more oxidative DNA damage genome wide. These unexpected results triggered us to characterize further Neil-deficient mice to address the impact of Neil DNA glycosylases in health and disease, including studies of cognition, behavior (e.g., anxiety and activity, neurogenesis, neuroprotection) and cardiovascular disease.

Biography:
Prof Magnar Bjørås is a Principle Investigator of the research group of Cellular responses to DNA damage at Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU), Trondheim and at Department of microbiology Oslo University Hospital/University of Oslo. The main focus of the Bjørås group has been on repair of endogenous DNA base lesion repair mechanisms and genome stability. He has made major contributions to characterization of many new DNA repair enzymes from bacteria, yeast and mammalian. He spent 2.5 years (2002-2004) in Professor John Tainer's lab at Scripps Research Institute, California. His research group has solved the atomic structure (3D) of many DNA-protein complexes revealing several new mechanisms of DNA base damage recognition and catalysis . The last 15 years he has established research on the role of DNA base lesion repair in neurodegeneration, cognition and behavior, which is a new direction in the DNA repair field revealing novel functions beyond canonical DNA repair. Bjørås has established collaborations with clinicians to study the impact of DNA base lesion repair on diseases such as infections, heart failure, metabolic diseases and cancer.

Name: Hilde Nilsen
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Speaker: Hilde Nilsen
Title: Mithormesis promotes dopaminergic neuron health in Base Excision Repair deficient C. elegans

Abstract:
Tanima SenGupta, Konstantinos Palikaras, Henok Kassahun, Alfonso Schiavi, Silvia Maglioni, Lars Eide, Nektarios Tavernarakis, Natascia Ventura, Hilde Nilsen
Oxidative stress and mitochondrial dysfunction are implicated in most common neurodegenerative diseases. Oxidation of DNA bases is an inevitable consequence of oxidative stress that requires thebase excision repair (BER) pathway for repair. Yet, good experimental evidence to prove that DNA damage and its repair by BER also contributes causally to common, age related neurodegenerative diseases is lacking. To better understand how BER affects aging phenotypes, we study the C. elegansnth-1 mutant, which lacks NTH-1 DNA glycosylase, the only enzyme dedicated to repair of oxidative DNA base damage via the BER pathway. We recently showed that nth-1 mutants have mitochondrial dysfunction characterised by lower mitochondrial DNA copy number, reduced mitochondrial membrane potential, and increased steady-state levels of reactive oxygen species. Consistently, nth-1mutants express markers of chronic oxidative stress with high basal phosphorylation of MAP-kinases (MAPK) in the germline. Here, we will present new data that suggest that mithormesis protects dopaminergic neurons from age-related degeneration.

Biography:
Positions held
2013 - present: Professor Department of Clinical Molecular Biology
2009 - 2013: Assistant Director, Biotechnology Centre of Oslo.
2006 - present: Problem-based learning supervisor, Medical Faculty, University of Oslo.
2004 - 2013: Group leader, “DNA Repair”, Biotechnology Centre of Oslo.
Education
2000 - 2004: Post doctoral fellow, Cancer Research UK.
2000: Dr. ing. from the Norwegian University of Science and Technology (NTNU), Trondheim, Norway
Research Interests
We are interested in the quality control mechanisms that maintain function of DNA and RNA throughout the lifetime of cells and organisms.
DNA repair enzymes remove damaged or inappropriate bases from DNA. Historically, studies of DNA repair has been motivated by the need for these mechanisms in order to prevent mutations - changes in the genetic code. Studies of DNA repair is therefore important in order to understand how cancer develops and how cancer can be treated. In recent years it has become clear that DNA repair enzymes have many important functions in cells other than to prevent mutations, most importantly in neurobiology to prevent neurodegenerative diseases. We have also recently demonstrated that some DNA repair proteins also contribute to RNA quality control.
Aims:
To study whether DNA damage and mutations may act as a driver of tumorigenesis
To study how DNA repair mechanisms protect us from premature aging and age-related neurodegenerative diseases
To study how DNA repair proteins contribute to RNA quality Control

Name: Arne Klungland
Institute: Oslo University Hospital and University of Oslo
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Speaker: Arne Klungland
Title: Epitranscriptomic regulation neurodevelopment

Abstract:
A broad repertoire of modifications is known to underlie adaptable function of proteins, DNA and RNA. Methylations of DNA and histone residues regulate transcription and the discoveries of demethylases that remove methylation in DNA and histones has led to a tremendous progress in the understanding of dynamic methyl marks in gene regulation (Feinberg, Nature 2007, 447:433-40, Shi et al., Cell 2004, 119:941-53). Post-transcriptional RNA modifications were identified several decades ago, but the reversible nature of RNA modifications has only recently been discovered (Jia et al., Nat Chem Biol 2011, 7:885-7; Zheng et al., Mol Cell 2013, 49:18-29). Our studies will focus on the role of readers and erasers of these dynamic methyl marks.
We and others have recently shown that a particular mark, N6-methyladenine (m6A) is highly prevalent and dynamically regulated in the brain. Furthermore, writers, readers and erasers of m6A is required for healthy neuronal development (Yoon et al., Cell 2018, 171:877-889; Li et al., Genome Biol 2018, 19:69). For example, we demonstrate that neural stem/progenitor cell (NSPC) self-renewal and spatiotemporal generation of neurons and other cell types are severely impacted by the loss of Ythdf2, a reader of m6A, in embryonic neocortex. Despite the many novel finding on m6A dynamics in neuronal development and brain function, the understanding of regulatory mechanisms is still in its early stages.

Biography:
Prof Arne Klungland is head of research at Section for Molecular Medicine at Oslo University Hospital. He did his PhD and post doctoral training with Erling Seeberg at the University of Oslo and Tomas Lindahl at Cancer research UK in London, two pioneers in the early work of DNA repair. In 2000 he had a sabbatical stay with Jean-Marc Egly at IGBMC, Strasbourgh. He started his scientific career working on DNA base excision repair (BER) and has later focused on epigenetic and epitranscriptomic regulation of the early embryo and in the developing brain.

Prof Klungland and published more than 100 papers and has several publications in *PNAS*, *EMBO J*, *Nature Comm*, *Mol Cell*, *CELL and Nature*, *etc*. Klungland received the 2018 Excellent Researcher Award for Oslo University Hospital.

Name: Minoru Takata
Institute: Radiation Biology Center, Graduate School of Biostudies, Kyoto University
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Speaker: Minoru Takata

Title: Endogenous DNA damage as revealed by studying Fanconi anemia

Abstract:

Fanconi anemia (FA) is a devastating hereditary disorder with impaired genome stability resulting in physical abnormalities, gradual loss of hematopoietic stem cells, and development of tumors and leukemia. It has been suggested that functions of FA genes are required to exert normal levels of DNA repair by homologous recombination, and to maintain genome stability by counteracting endogenous metabolites, such as aldehydes, that damage DNA and stall replication forks. Recent studies have also implicated co-transcriptional R-loops, consisting of a DNA:RNA hybrid and displaced single stranded DNA, as one of the potential endogenous sources that induce genome instability and the FA phenotype. Furthermore, the key FA protein FANCD2 has been shown to prevent degradation of stalled replication forks. In this talk, I will show some of our recent work that highlight the important endogenous DNA damage which is handled by the FA pathway to maintain genome stability.

Biography:
Dr Minoru Takata is investigating the molecular mechanisms of DNA damage response and Fanconi anemia. He graduated from a medical school and trained for ~10 years as a physician. Then he thought he would like to devote his efforts to elucidating disease mechanisms and started a carrier as a molecular biologist. After spending posdoc years in a lab (Dr Tomohiro Kurosaki) in the US, he moved to Kyoto University (Professor Shunichi Takeda) and since then he has been in the field of DNA repair, DNA damage response and homologous recombination. He worked as a professor in three different Japanese universities so far, and now belongs to Radiation Biology Center, Graduate School of Biostudies, Kyoto University (Japan).

References:
Minako Mori, Asuka Hira, ..., Minoru Takata. Pathogenic mutations identified by a multimodality approach in 117 Japanese Fanconi anemia patients. **Haematologica** in press (2019)
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Histone chaperone activity of Fanconi anemia proteins, FANCD2 and FANCI, is required for DNA crosslink repair. Sato K, ..., Takata M, Kurumizaka H. **EMBO J**. 2012 Jul 24;31(17):3524-36.

Name: Jian XIAO
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Speaker: Jian XIAO
Title: Enhanced neuroprotection with drug deliver system containing bFGF in Parkinson's disease rat model

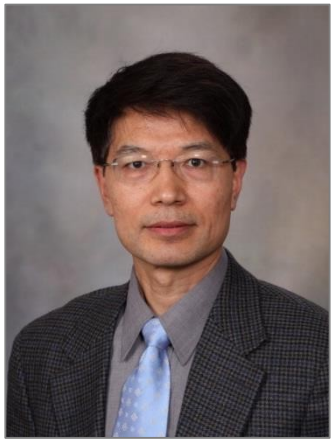
Abstract:

We demonstrated that basic fibroblast growth factor (bFGF), as a neurotropic factor, inhibited ER stress-induced neuronal cell apoptosis and that 6-hydroxydopamine (6-OHDA)-induced ER stress was involved in the progression of PD in rats. However, the poor stability and short half-life of bFGF, have hampered its clinical use for neurological diseases, thus we developed some strategies to controlled Release bFGF. We modified native recombinant bFGF by covalently attaching polyethylene glycol (PEG) polymers, named PEGylation, to enhance its neuroprotection efficacy in PD model. A decellularized brain extracellular matrix (dcBECM) containing bFGF showed the highest cell survival rate of PD model cells, improved behavioral recovery and positive expressions of neurotrophic proteins in PD recovered rats. We also developed a new phospholipid-based gelatin nanoparticles encapsulating bFGF to target the brain via nasal administration. The intranasal gelatin nanostructured lipid carriers (GNLs) efficiently enriched exogenous bFGF in olfactory bulb and striatum without adverse impact on the integrity of nasal mucosa and showed obvious therapeutic effects on hemiparkinsonian rats. The combination of drug deliver system and bFGF would be a promising therapeutic strategy to realize an effective and safe alternative for PD treatment.

Biography:

Professor Xiao is Vice Director of Key Laboratory of Biotechnology and Pharmaceutical Engineering of Zhejiang Province, Vice Dean of School of Pharmaceutical Sciences, Wenzhou Medical University. Prof. Xiao works as the editorial board member of Biomed Res Int.

Professor Xiao has committed himself to scientific research and applied Research for 10 years in wound repair. Based on the background of skin wound healing and nerve injury repair by growth factors, he launched a series of research and published 80 papers (as first, or co-first and corresponding or co- corresponding author); H index 21; 1600 times cited). He also got 10 patents of invention, 1 new drug license and 1 medical device license. His major achievements are: 1, discovered that the mechanisms of fibroblast growth factor (FGF) in skin wound healing are acceleration of wound closure, inhibition of scar formation, decrease pigmentation, and promotion of hair growth, demonstrated that FGF stimulate skin functional repair. His studies also proved that FGFs exert the bioactivity including neuronal protection, axon regeneration, and inhibition of glial scarring.repair of spinal cord injury, which contribute to the functional recovery of spinal cord injury (SCI). 2, developed several biomaterials which can improve the release and efficacy of FGFs to treat skin wound and SCI, proposed a new theory for design the biomaterials to encapsulate growth factors. In particular, he won the first class National Award of Science and Technology (2015), the second class National Award of Science and Technology (2018).



Name: Jinsan ZHANG
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Speaker: Jin-San ZHANG
Title: The AMPK-Parkin axis negatively regulates necroptosis-induced inflammation by inhibiting the necrosome

Abstract:
The receptor-interacting protein 1 (RIPK1)/RIPK3 kinases play important roles in necroptosis that is closely linked to inflammatory response. Although the activation of necroptosis is well characterized, how necroptosis is tuned down is largely unknown. Here, we found that Parkin (also known as PARK2), an E3 ubiquitin ligase implicated in Parkinson's disease and a tumor suppressor, regulates necroptosis and inflammation by regulating necrosome formation. Parkin prevents the formation of the RIPK1-RIPK3 complex by promoting polyubiquitination of RIPK3. Parkin is phosphorylated and activated by the cellular energy sensor AMP-activated protein kinase (AMPK). Parkin-deficiency potentiates the RIPK1-RIPK3 interaction, RIPK3 phosphorylation, and necroptosis. Importantly, Parkin deficiency enhances inflammation and inflammation-associated tumorigenesis. These findings demonstrate that the AMPK-Parkin axis negatively regulates necroptosis via inhibiting the RIPK1-RIPK3 complex formation and this regulation may serve as an important mechanism to fine-tune necroptosis and inflammation.

Biography:
Dr. Zhang obtained both his M.D. and Ph.D at Norman Bethune College of Medicine, Jilin University in Changchun, China (1992). He then received National postdoctoral fellowship training at the National Laboratory of Medical Molecular Oncology, Chinese Academy of Medical Science, after which he became a faculty member, an Associate Professor (1995) at the National Laboratory of Medical Molecular Biology, Peking Union Medical College. He joined Mayo Clinic in 1997 as a senior research fellow, became an Assistant Professor and a faculty at the Department of Gastroenterology in 2002, and Research Scientist at the Division of Oncology Research, Schulze Center for Novel Therapeutics in 2008. Dr. Zhang got recruited to WMU in 2014 and established the Cell Signaling and Epigenetics Research Laboratory at the School of Pharmaceutical Sciences. He also co-directs the Center for Precision Medicine, the First Affiliated Hospital of WMU(2016-), and International Collaborative Center on Growth Factor research(2018-). His labs have been interested in basic cancer biology including mechanisms of cell signaling, epigenetic regulation, as well as fibroblast growth factors in development and regeneration/repair.

Name: Tormod Fladby
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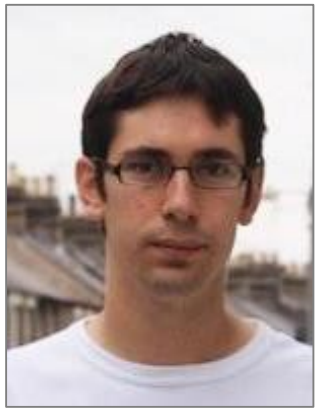
Speaker: Tormod Fladby
Title: Synapse integrity and pre-dementia glial activation patterns

Abstract:
Alzheimer's disease (AD) may be described as a biological continuum that includes the hallmark pathological processes of amyloid-beta (Aβ) dysmetabolism, formation of amyloid deposits (A), neurofibrillary tangles (T), neurodegeneration (N), determined by measuring cerebrospinal fluid (CSF) levels of Aβ42, phosphorylated tau (P-tau), and total tau (T-tau) respectively. The presence or absence of pathological markers can be summarized as an A/T/N score, an unbiased classification of pathology and severity along the AD continuum.
Neuronal and glial cell interaction is essential for synaptic homeostasis and may also be affected in Alzheimer's disease (AD). Glial activation occurs as part of altered immune cytokine activities, which also change towards increased inflammatory activity during AD progression. However, micro- and astroglial activation are interlinked, and genetic evidence suggests that innate immunity could be a prime mover in the AD cascade.
Soluble TREM2 is released upon microglial activation, leading to increased levels of CSF sTREM2 in AD. However, microglial activation per se does not need to be inflammatory, but may be a compensatory response at the synapse. Here we study how microglial activation markers relate to markers for neural and syanptic integrity in pre-dementia AD.

Biography:
Tormod Fladby is a professor at the University, of Oslo head of the Department of Neurology at Akershus University Hospital (Ahus) (which has > .5 mill. populatin within its catchment area). He has an academic background in neurobiology and neurology, a research background in Cognitive Neuroscience using a broad spectre of methodfs within advanced imaging (MRI and PET), neuropsychology and proteomics as well as informatics.

TF leads the Cognitive Neuroscience Group at Ahus, and Norwegian national and European (EU JPND) reserach efforts within the field of prodromal dementia diseases. As part of this process a customized database has been established, with extensive standardized clinical, genetic, imaging, proteomic and cognitive data with a corresponding reserach biobank.



Name: Dr Will McEwan
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Speaker: Will McEwan
Title: The intracellular antibody receptor TRIM21 enables selective degradation of proteins relevant to neurodegeneration

Abstract:
Gene editing and RNA intereference techniques enable the selective depletion of genes at the nucleotide level. To date there are no mechanisms that enable the degradation of genes at the protein level. We identified a novel antibody receptor, TRIM21, which, uniquely among antibody receptors, is expressed in the cytoplasm. Upon encountering intracellular immune complexes, TRIM21 stimulates a rapid degradation response at the proteasome. This activity provides a last line of defence against infection during in vivo viral challenge. We recently demonstrated that TRIM21 can be repurposed against host proteins to enable the acute and selective depletion of intracellular proteins. We have developed this as a research technique, termed TrimAway, to enable broadly-applicable protein-level knockdown. The aggregation of tau is a pathological characteristic of several neurodegenerative diseases including Alzheimer's disease. We show that assemblies of tau that act as 'seeds' can import antibody to the cell whereupon TRIM21 stimulates their inactivation. This provides proof-of-principle for the cytoplasmic inactivation of disease-relevant proteins in the intracellular domain.

Biography:
Will McEwan studied Genetics BSc at UCL and undertook his PhD at the University of Glasgow under the supervision of Prof Brian Willett on the detection of lentivirus infection by the cytoplasmic sensor TRIM5. In 2009, he joined the lab of Dr Leo James as a postdoc at the MRC Laboratory of Molecular Biology, Cambridge, UK. Here he co-discovered TRIM21 as an antibody receptor and characterised its degradation and signalling activities (Mallery et al 2010 PNAS; McEwan et al 2012 J Virol; McEwan et al 2013 Nat Immunol). He also maintains an interest in lentivirus research contributing to the discovery of dNTP import to the HIV-1 capsid (Jacques et al 2016).

In 2017 Will McEwan was awarded a Sir Henry Dale Fellowship by the Wellcome Trust and Royal Society to extend findings that cellular proteins, including tau seeds, can be targeted by intracellular antibodies via TRIM21 (McEwan et al 2017 PNAS; Clift et al 2017 Cell). His group is hosted within the UK Dementia Research Institute at the University of Cambridge, UK.

Speaker: **Linda Hildegard Bergersen**
Title: Physical activity halves the risk of getting Alzheimer's disease

Abstract: Age-associated cognitive impairments like Alzheimer's disease (AD) are becoming the major health problem worldwide, increasing as the proportion of old age individuals increases. There is no disease-modifying or other effective treatment available. Physical exercise significantly reduces the risk of developing AD with **nearly 50%,** delays functional deterioration in AD patients, and counteracts cognitive decline in old age also independent of AD. In mouse models of AD, physical activity arrests cognitive impairment and stops progression of brain AD pathology. However, how exercise brings about these changes has not been clear. Lactate increases dramatically in intense exercise, to levels that stimulate the lactate receptor HCAR1 (GPR81), which my laboratory discovered to be present and active in brain. Our suggestion that HCAR1 activation counteracts the development of Alzheimer's disease derives from our recent discovery that activation of the lactate receptor HCAR1 increases the growth factor Vascular Endothelial Growth Factor (VEGF) and increases the density of blood capillaries in hippocampus, the brain region allowing new memories to be stored. VEGF stimulates the formation of blood vessels (angiogenesis) and promotes the formation of new neurons (neurogenesis) and changes of nerve contacts (synaptic plasticity) allowing learning in addition to being neuroprotective.

Name: **Linda H. Bergersen**
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Biography: Professor Linda Hildegard Bergersen has pursued research on physical exercise since her days as MSc student. Bergersen first breakthrough (2001) in the brain-lactate field came as a PhD student at the University of Oslo when she discovered for the first time that the lactate transporter MCT2 was localized at the postsynaptic density of excitable neurons in the brain. During this period Bergersen did pioneering work on the localization of several lactate transporters in the brain. During her postdoc period (2002-2004) she worked one year in the laboratory of Professor Pierre Magistretti in Lausanne, Switzerland. Bergersen established her own research group named **the Brain and Muscle Energy Group** at the Medical Faculty, University of Oslo in 2004. Initially, Bergersen's focus has been on energy failure in the brain, *inter alia* determining the role of lactate transporters in brain diseases, but also investigating mitochondrial dysfunction and impaired DNA repair in neurodegeneration. Since 2012 the main focus of her group's research has been on the G-protein coupled lactate receptor, HCAR1 (GPR81), in the brain. In recent breakthrough original papers Bergersen's group discovered the **lactate receptor to be present and active and crucial for vascularization in the brain, opening new opportunities for basic and translational research.** Currently Bergersen's group main projects are on brain diseases leading to cognitive decline like Alzheimer disease (AD) and possible treatments to rescue the decline.

Name: Evandro F. Fang
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Speaker: Evandro F. Fang
Title: Targeting on mitophagy and NAD⁺ to extend human healthspan and lifespan

Abstract:
There were 962 million elderly (60+) globally in 2017, and this number will rise to 2.1 billion in 2050, bringing formidable healthcare and socio-economic challenges. Aging is arguably the highest risk factor for numerous human diseases, thus understanding the molecular mechanisms of human aging holds the promise to develop interventional and therapeutic strategies for many diseases all at once, promoting healthy longevity.

Accumulation of damaged mitochondria is a hallmark of human aging and age-related neurodegeneration, including Alzheimer's disease (AD). However, the molecular mechanisms of the impaired mitochondrial homeostasis and their relationship to AD are still elusive. Mitophagy is a cellular self-clearing process of damaged and superfluous mitochondria, thereby plays a fundamental role in maintaining neuronal function and survival. We hypothesize that defective mitophagy causes accumulation of damaged mitochondria, which further in combination with the two main AD causative factors, Aβ plaques and tau tangles, exacerbating AD progression. Restoration of mitophagy through upregulation of cellular NAD+, a primary cofactor in human health and life, forestalls pathology and cognitive decline in C. elegans and mouse models of AD. In view of the physiological feature of NAD+ in human, our study suggests immediate interventional/therapeutic potential for both normal ageing and age-related memory loss.

Biography:
Dr. Evandro F. Fang is investigating the molecular mechanisms of one of the most fundamental and fascinating topics in current biology: human aging. After finished his Ph.D. training in Biochemistry at the Chinese University of Hong Kong in 2012, he started a 5-year postdoctoral fellowship at the National Institute on Aging USA with Dr. Vilhelm Bohr. At the same time, he also worked closely with Prof. Mark Mattson on extensive trainings and research of neuroscience. In September 2017, he established his independent laboratory at the University of Oslo, Norway. His laboratory is focused on the molecular mechanisms of how cells clear their damaged and aged mitochondria, a process called "mitophagy", as well as the roles of mitophagy in Alzheimer's disease (AD). NAD^+ is a fundamental molecule in life and health, and he is investigating the molecular mechanisms on how NAD^+ inhibits ageing and age-predisposed neurodegeneration, especially AD. He is fascinated with and actively engaged in moving his laboratory findings to translational applications, with the overarching goal to establish novel and safe biological approaches to promote longer and healthier human lives.

He has published over 55 papers in peer-reviewed journals including papers in Cell, Cell Metabolism, Nature Reviews MCB, and Nature Neuroscience. He has received several awards including The NIH Fellows Award for Research Excellence 2014, 2015, and an awardee of the prestigious Butler-Williams Scholar on Aging 2016 (USA), an FRIMEDBIO Young Research Talent 2017(Norway), and a finalist of the 2017 ERC Starting grant.

Name: Hansang Cho
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Speaker: Hansang Cho
Title: 3D Human Brain models in Microfluidics for the Study of Neurological Disorders

Abstract:
With hundreds of billions of neurons and thousands of trillions of synaptic connections between them, the human brain is the most complex system on earth. However, there are no well-developed human brain models to study the brain activities in either laboratory environments or in animal bodies. Here, I present micro-scaled 3D environments that reconstruct a 3D human brain in Alzheimer's disease (AD) by recapitulating AD signature of elevated levels of amyloid-beta (A-beta), tau proteins, activation of microglia, immune cells resident in a central nervous system (CNS), and consequent neuronal damage. In particular, the model mirrored microglial neurotoxic activities such as axonal cleavage and neurotoxic release.

Biography:
Dr. Cho's research focuses on organ-on-chips, nanomedicine for the study of neurosciences and cancer biology, innovative mechanical components evolving multiple physics, and portable platforms for healthcare diagnostics and environmental sustainability. He received his B.S. and M.S in Mechanical Engineering from Seoul Nat'l University, Ph.D. in Bioengineering from University of California at Berkeley, and a postdoctoral training at Harvard Medical School. He received Cure Alzheimer's Fund award, CRI Duke Energy Special Initiatives Funding award, Lawrence scholar program fellowship from Lawrence Livermore National Laboratory, Fellowship supported by Intel Inc., Study Abroad Scholarship by the Korean National Institute for International Education.

Dr. Cho has been productive with publications in *Nature Neuroscience*, *Nature Communication*, *Nano Letters*, *and ACS Nano etc*.

Name: Leiv Otto Watne
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Speaker: Leiv Otto Watne
Title: Molecular linkages of delirium to dementia

Abstract:
Abstract
Delirium is state of "acute confusion" with sudden impairment in awareness and cognition, and is a common and severe complication to acute somatic illness. The point prevalence of delirium in a general hospital is estimated around 20 %. Patients with dementia are at particularly high risk. Despite being a major public health concern, delirium is severely understudied and the pathophysiology of delirium is poorly understood.

There is now strong evidence that delirium has the potential to precipitate dementia in patients that are cognitively intact, and to induce a more rapid pace of deterioration in those already demented. It has been hypothesized that delirium and dementia share pathophysiological features. Thus, delirium may represent a window into the complex pathogenesis of dementia.

Biography
Leiv Otto Watne is the leader of Oslo Delirium Research Group at the University of Oslo. His main research interest is human CSF/blood studies in delirium.

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Speaker: Jens Pahnke
Title: Blood-brain barrier transport in aging and neurodegeneration

Abstract:
All treatment studies against Alzheimer's disease (AD) or mild cognitive impairment failed so far.
What is the reason for that?
Ninety-nine percent of all AD patients develop the sporadic form of the disease that is not linked to any of the known genes of familiar AD. Familiar AD is a disease that is caused by an overproduction of a toxic peptide (Abeta) due to problems in degradation of a larger, complex transmembrane protein called APP. The toxic Abeta accumulation leads to further devastating effects finally resulting in the dead of neurons and the clinical sign of dementia with memory deficiency, orientation problems, speech abnormalities, behavioural changes and many more.
Treatment trails aimed so far in reducing overproduction or destroying aggregates in the brain. These tests aimed in either reducing the production with chemicals or increasing the removal of plaques by antibody treatment, so called AD vaccination.
We have been working on another major general problem of dementia and aging: the brain vessels and the blood-brain barrier since AD is accompanied by major vascular problems.
The blood-brain barrier hosts important active transport molecules that can be used for diagnostics and treatment of dementia and neurodegenerative disease in general. These transport molecules, ABC transporters, are known from cancer research and treatment since the 1970ies.
We have discovered that some of these transporters are impaired in the brain's vessels and thus lead to increased amount of toxic peptides resulting in aggregation and storage. Activation of ABC transporters can be used for treatment and diagnostics.
The presentation will describe the mechanisms and explain possibilities for diagnostics and treatment of patients with dementia and movement disorders. These treatments are currently under exploration in patients.

Biography:
Jens Pahnke is both a medical doctor and a molecular biologist by training, working as a specialist and head of neuropathology in Oslo. His lab develops new treatment and diagnostic tools for patients with dementia and motor diseases. His focus of research are the brain's waste disposal transporters that excrete toxic metabolites and peptides from the brain.
His lab was the first in 2010 to discover the importance of ABCC1 for the pathogenesis of sporadic AD. This gene was now also found in an inherited form of AD in a family. The drainAD study is currently performed to test a chemical activating compound in AD patients for diagnostics and treatment.
Using medicinal plants he develops treatment that is used to treat Alzheimer's disease, amyotroph lateral sclerosis (ALS), fronto-temporal lobe degenerations (FTLDs), Huntington's disease (HD) and neuronal ceroid lipofuscinoses (NCL, a childhood dementia). Specific medical plants extract from St. John's wort (Hypericum perforatum) and Greek ironwort (Sideritis scardica) are used currently as Renovare500® to deliver therapy to the patients with neurodegenerative diseases.
His lab is renowned for its work on blood-brain barrier ABC transporters and the development of new humanised mouse models for dementia research. Jens Pahnke won several research awards and is the current president of the Scandinavian Society of Neuropathology . He is Professor at the Universities of Oslo, Riga, Lübeck, and the Leibniz-Institute for Plant Biochemistry in Halle/ Germany and lecturer at the German University in Cairo.