The NO-Age and NO-AD Seminar Series 004

‘From Pathological Ageing to Healthy Longevity’

13:30-16:30, Wednesday 15th April 2020
Room Møterom L-200, Domus Medica, UiO
Sognsvannsveien 9, 0372 Oslo
All welcome, no registration

Organizers:
Evandro F. Fang, Jon Storm-Mathisen (Queries: e.f.fang@medisin.uio.no)

Speakers

Prof. Jeorge Martin
University of Washington
Seattle, USA

Prof. Lynne Cox
University of Oxford
UK

Prof. Morten Scheibye-K.
Copenhagen University
Denmark

Dr. Ingrid Åmellem
University of Oslo
Norway

Ruben Gudmundsrud
University of Oslo and AHUS
Norway

Rebecca Presterud
University of Oslo and AHUS
Norway

The NO-Age and NO-AD Seminar Series 004

Keynote Lecture

'Highlights of a 60+ Year Journey in the Gerosciences'

by

Prof. George M. Martin, MD

University of Washington, Seattle, WA

at

13:30-15:30, Wednesday 15th April 2020

Room Møterom L-200, Domus Medica
Sognsvannsveien 9, 0372 Oslo
The University of Oslo, Norway

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The NO-Age and NO-AD Seminar Series 004

Modifying ageing in Werner syndrome and its relevance to normal human ageing

by

Assoc Prof Lynne Cox
University of Oxford, UK

at

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‘Accelerated aging and the quest for interventions’

by

Assoc. Prof. Morten Scheibye-Knudsen

Copenhagen University, Denmark

at

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The NO-Age and NO-AD Seminar Series 004

‘Treating Alzheimer’s disease with lactate by activation of Hydroxycarboxylic acid receptor 1’

by

Postdoc Ingrid Åmellem
The University of Oslo

at

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The NO-Age and NO-AD Seminar Series 004

'Targeting the NAD$^+$-mitophagy axis to fight against premature ageing and normal ageing'

by

Mr. Ruben Gudmundsrud

University of Oslo and the Akershus University Hospital

at

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'xxx'

by

Ms. Rebecca Presterud

University of Oslo and the Akershus University Hospital

at

13:30-15:30, Wednesday 15th April 2020

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Organizers:
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Name: Prof. George M. Martin, MD
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Speaker: Professor George M. Martin
Title: Highlights of a 60+ Year Journey in the Gerosciences

Abstract:
My journey started as a pathologist who was struck by the marked variability of patterns of disease seen in geriatric autopsies. This led to genetic approaches to aging research, starting with the search for the mutations responsible for the Werner Syndrome and other Segmental Progeroid Syndromes and the discovery that virtually all resulted in genomic instability. I then founded one of the first US Alzheimer's Disease Research Centers, leading to the mapping of two early onset forms caused by dominant mutations (PS1 & PS2) and the cloning of PS2. My lab is currently testing the hypothesis that age-related increases in variegated gene expressions can be considered as the newest member of the Hallmarks of Aging. Our most recent publication (PMID: 31957802) describes initial research documenting roles for specific human genetic loci to either greatly increase or decrease VGE in an initial test locus of relevance to aging, Sirt1.

Biography:
Professor of Pathology Emeritus (Active); Director Emeritus, Alzheimer's Disease Research Center; Adjunct Professor of Genome Sciences (Retired), University of Washington ; Visiting Scholar, Molecular Biology Institute, UCLA. Dr. Martin received his BS and MD degrees from the University of Washington and has been a member of its faculty since 1957. After an internship at the Montreal General Hospital and a residency in anatomic pathology at the University of Chicago, he pursued postdoctoral research in somatic cell genetics under Professor Guido Pontecorvo at Glasgow University, where he worked with Aspergillus nidulans and human cell cultures. Other postdoctoral experiences have included research in molecular biology with Francois Gros in Paris and in experimental embryology with Henry Harris and Richard Gardner at Oxford University. He has also done medical genetics fieldwork in India. Honors for his research have included the Brookdale, Kleemeier and Paul Glenn Foundation awards of the Gerontological Society of America, the Allied-Signal Corporation Award, the Irving Wright Award of the American Federation for Aging Research, the American Aging Association Research Medal and Distinguished Scientist Award, the Pruzanski Award of the American College of Medical Genetics, and a World Alzheimer Congress Lifetime Achievement Award. He has also received an Outstanding Alumnus Award from the University of Washington School of Medicine. He was elected to the Institute of Medicine of the National Academy of Sciences and now serves as a Senior Member. Dr. Martin was a member of the National Advisory Council, the Board of Scientific Counselors of the National Institute on Aging, and the Scientific Advisory Board of the Ellison Medical Foundation. He currently serves as the Scientific Director of the American Federation for Aging Research. He was the Founding Editor-in-Chief of an AAAS/Science WEB site for research on the biology of aging (SAGE KE). Dr. Martin is a Past President of the Tissue Culture Society of America, American Federation for Aging Research and the Gerontological Society of America.

Dr. Martin's research has for many years been concerned with the development of genetic approaches to the study of aging and age-related diseases in mammals. One theme has been the plasticity of the genome of somatic cells. His lab has contributed to our understanding of a number of mechanisms for the heritable alteration of genetic information (Nature, 1967; Science , 1969). During this period a parallel series of biochemical, cytogenetic and somatic cell genetic studies on cells from aging mammals addressed various somatic mutational theories of aging; these have demonstrated the importance of relatively large scale chromosomal types of mutation. An offshoot of this work provided the first data on mutation frequencies in human epithelial cells in aging human subjects (Human Mol Genet, 1996).

These studies were reinforced by a long series of investigations of a remarkable human progeroid syndrome, the Werner syndrome, a recessive mutation that Dr. Martin's group and Japanese investigators mapped to chromosome 8. This led to the positional cloning of the Werner syndrome gene and its identification as a member of the RecQ helicase family (Science, 1996). Dr. Martin and colleagues have provided molecular evidence for the importance of intragenic deletions in the somatic cells of Werner syndrome subjects (Proc Natl Acad Sci USA, 1989). Cells from these patients were also shown to undergo accelerated "aging in vitro" (Lab Invest, 1970). This latter line of research provided the first evidence for the limited replicative potential of cells of the vascular wall (Exp Mol Path, 1973). Together with Drs. Tom Norwood and William Pendergrass, the Martin lab also carried out the first cell fusion experiments for the investigation of dominance/recessivity relationships between old cells, young cells and "immortal" cells (Proc Natl Acad Sci USA, 1974; J Cell Biol, 1975) and demonstrated that the decline of growth potential involved gradual and variable attenuations of clonal growth (Am J Path, 1974).

Later in his career, Dr. Martin turned his attention to mechanisms of the aging of post-replicative cells, again using genetic approaches. He assembled a team of investigators to carry out a linkage analysis of familial Alzheimer disease, an effort that led to the assignment of the commonest form to chromosome 14 (Science, 1992) and to the mapping and positional cloning of a related locus on chromosome 1 (Science, 1995). New candidate genes were sought using the yeast protein interaction trap methodology. This work has led to a series of papers on an adaptor protein (FE65) that is of importance in the modulation of the function of the beta amyloid precursor protein; polymorphisms at that locus were shown to play a role in the susceptibility to AD in very old individuals.

Dr. Martin is certified by the American Board of Medical Genetics (Clinical Cytogenetics) and the American Board of Pathology. His major teaching contributions at the University of Washington have involved the founding directorships of the Medical Scientist Training Program and the "Genetic Approaches to Aging Research" Institutional Training Grant of the National Institute on Aging. He continues to serve on the Executive Committee of that program and the Nathan Shock Center of Excellence for Basic Research on the Biology of Aging, both of which are under the directorship of his former graduate student, Prof. Peter S. Rabinovitch.

Name: Lynne Cox
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Speaker: Assoc Prof Lynne Cox

Title: Modifying ageing in Werner syndrome and its relevance to 'normal' human ageing

Abstract:

Progeroid syndromes have yielded informative insights into the mechanisms of human ageing. The causative gene in premature ageing human Werner syndrome (WS) is the dual function WRN helicase/exonuclease that has been implicated in many aspects of DNA metabolism. We have previously shown that DNA replication fork progression is defective in WS patient-derived cells and that this is likely to arise from Holliday junctions that form when replication forks stall or collapse in the absence of functional WRN, since ectopic expression of an HJ nuclease can correct the defect. Both fly and worm models of WS show marked DNA damage and anaphase bridges during mitosis, leading to high levels of illegitimate genomic recombination, premature ageing and shortened lifespan. However, the evidence that progeroid syndrome genes normally serve a role in preventing ageing is still at best only correlative. To test whether WRN can indeed improve ageing outcomes, we have generated transgenic *C. elegans* worms which overexpress the worm orthologue of WRN, *wrn-1*. We find that *wrn-1* overexpression not only corrects lifespan defects in *wrn-1*- mutant worms, but that overexpression in a wild type background extends lifespan significantly over than of control wild type animals. Moreover, *wrn-1* overexpression results in improved morphology, tissue integrity and movement throughout the life course - the first demonstration that a progeroid-associated gene product is effective in delaying ageing pathologies. Hence we conclude that *wrn-1* protects against ageing phenotypes and moreover that normal levels may be limiting for lifespan and health, with significant implications for human ageing.

Biography:
I received my BA, MA and PhD in Natural Sciences at the University of Cambridge, then carried out post-doctoral work in Dundee with Prof Sir David Lane. I was awarded a Royal Society of Edinburgh Research Fellowship to progress her independent research, and from this, developed initial IP for the spin-out Cyclacel (https://www.cyclacel.com). I hold a Fellowship at Oriel College, Oxford, and an Associate Professorship at the Department of Biochemistry, University of Oxford, and co-founded the Oxford Ageing Network, OxAgeN, which now forms part of the Oxford-wide ageing research collaboration hub (ARCH, https://www.archub.ox.ac.uk).

I am a Trustee of the British Society for Research on Ageing, Fellow of the Royal Society of Biology, panel member of the UK Biochemical Society's Clinical and Translational theme, primary international member of the Norwegian NO-Age consortium, and I have just been elected co-chair of a new EU special interest group of the European Geriatric Medicine Society on the biology of ageing. In 2015, I received the US Glenn Foundation award for research into the biological mechanisms of ageing, presented at the House of Lords (UK Parliament). I am a scientific advisor to the All-Party Parliamentary Group on Longevity; we launched our national strategy report on 'Healthier Lives for All' with the UK's Secretary of State for Health in February this year, with the ambitious aim of increasing healthy life expectancy by 5 years for the UK population by 2035.

My lab studies the molecular and cellular basis of ageing to identify specific biochemical processes and pathways that change as cells and organisms age. We are interested in both 'normal' and accelerated ageing, studying cellular senescence, a process which may underpin serious age-related diseases, and premature ageing Werner syndrome. We identified a DNA replication defect in patient-derived WS cells that could be corrected by Holliday junction resolution, and studies are ongoing to attempt to modulate premature senescence in human WS. In collaborative projects with Dr Robert Saunders (Open University) and Prof Alison Woollard (Biochemistry, Oxford), we have developed whole organism models of Werner syndrome in fruit flies and the nematode worm *C. elegans*, allowing integration of data from molecular biology and biochemical studies with whole animal biology. Our aim is to develop interventions that act on biological ageing processes to alleviate or even prevent age-related disease.

Name: Assoc. Prof. Morten Scheibye-Knudsen

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Speaker: Assoc. Professor Morten Scheibye-Knudsen

Title: Accelerated aging and the quest for interventions

Abstract:
Aging is characterized by an accumulation of DNA damage, likely contributing to the many pathologies observed in the elderly population. Indeed, recent findings suggest that we can intervene in the DNA damage response and thereby alleviate features of aging. In this lecture, I will describe our in silico, in vitro and in vivo methodologies aimed at understanding the physiological consequence of DNA damage, and how we can use this knowledge to develop interventions. This will be illustrated by our discovery of a new premature aging disease characterized by defects in DNA metabolism, and by our efforts to develop small molecule DNA repair stimulators. Our goal, is to allow everyone to live healthier and longer lives.

Biography:
Morten Scheibye-Knudsen is an Associate Professor at the Department of Cellular and Molecular Medicine and at the Center for Healthy Aging (CEHA), University of Copenhagen. He did his MD at the University of Copenhagen and worked briefly as a physician in Denmark and Greenland before turning to science. He did his post-doctoral fellowship at Vilhelm Bohr's lab at the National Institute on Aging, National Institutes of Health, where he utilized state-of-the art approaches to understand how DNA damage contributes to aging. He discovered that neurodegeneration in several premature aging diseases is partly caused by hyperactivation of a DNA damage responsive enzyme called polyADP-ribose polymerase 1 (PARP1). This activation leads to loss of vital metabolites such as NAD+ and acetyl-CoA. Importantly, this discovery facilitated the realization that we can intervene in the aging process by inhibiting PARP1, augmenting NAD+ levels and increasing acetyl-CoA. In his own lab he continues to focus on understanding aging by combining machine learning based approaches with wet-lab analyses with the goal of developing interventions for age-associated diseases and perhaps aging itself.

Name: Ingrid Åmellem
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(Linda Bergersen group)

Speaker: Postdoc Ingrid Åmellem (Prof. Linda Bergersen group)

Title: Treating Alzheimer's disease with lactate by activation of Hydroxycarboxylic acid receptor 1

Abstract:
Alzheimer's disease is a progressive neurodegenerative disorder affecting brain areas that control memory and cognitive functions. There is no cure for Alzheimer's, and it is therefore a great need to identify interventions that can slow or stop progression. Physical activity can significantly reduce the risk of developing Alzheimer's disease and delay its development. Physical activity works primarily through increasing brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). We recently discovered that physical exercise stimulates the brain lactate receptor, Hydroxy-Carboxylic Acid Receptor 1 (HCAR1), which causes VEGF to increase and new blood vessels to be generated. During physical exercise, blood lactate reaches the brain and activates HCAR1. In this lecture, I will describe how we believe that activation of HCAR1 by lactate treatment may delay the progression of Alzheimer's disease by increasing angiogenesis and neurogenesis, and reduce inflammation in the brain of mice. This may lay the groundwork for new treatment of neurodegenerative diseases.

Biography:
Ingrid Åmellem is a postdoctoral researcher working in The Brain and Muscle Energy group lead by Linda H. Bergersen at the University of Oslo. She did her PhD at the Kavli Institute at NTNU in Trondheim and at Nanyang Technological University in Singapore with Professor Ayumu Tashiro, working with adult neurogenesis and depression. Next, she became interested in the beneficial effects of physical exercise on the heart and brain and worked at the Cardiac Exercise Research Group (CERG) at NTNU with Professor Ulrik Wisløff. She is now continuing her interest in the effects of physical exercise on the brain together with Linda H. Bergersen. Their focus is the use of lactate treatment as an alternative to physical activity to promote an healthy brain and increase cognitive performance throughout life. The group discovered that the brain has a lactate receptor (HCAR1 / GPR81) and that activation of this receptor leads to the production of angiogenic growth factor and formation of new blood vessels in the brain.

Name: Ruben Gudmundsrud
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(the Fang group)

Speaker: Ruben Gudmundsrud (Evandro F. Fang group)
Title: Targeting on the NAD^+-mitophagy axis to against premature ageing and normal ageing

Abstract:
Metabolic dysfunction is a primary feature of Werner syndrome (WS), a human premature aging disease caused by mutations in the gene encoding the Werner (WRN) DNA helicase. WS patients exhibit severe metabolic phenotypes, but the underlying mechanisms are not understood, and whether the metabolic deficits can be targeted for therapeutic intervention has not been determined. Here, we report impaired mitophagy and depletion of NAD^+, a fundamental ubiquitous molecule, in WS patient samples and WS invertebrate models. Our findings suggest that WRN regulates transcription of a key NAD^+ biosynthetic enzyme nicotinamide nucleotide adenylyltransferase 1 (NMNAT1). NAD^+ repletion restores NAD^+ metabolic profiles and improves mitochondrial quality through DCT-1 and ULK-1-dependent mitophagy. At the organismal level, NAD^+ repletion remarkably extends lifespan and delays accelerated aging, including stem cell dysfunction, in *Caenorhabditis elegans* and *Drosophila melanogaster* models of WS. Our findings suggest that accelerated ageing in WS is mediated by impaired mitochondrial function and mitophagy, and that bolstering cellular NAD^+ levels counteracts WS phenotypes.

Biography:
Ruben Gudmundsrud is studying his master programme with associate Professor Evandro F. Fang at the University of Oslo and the Akershus University Hospital, Norway. By working with the Fang group postdoc Dr. Sofie Lautrup, they use fruit flies as a model system to unveil the molecular mechanisms of Werner syndrome (WS) and normal ageing. His major research interests focus on how different hallmarks of ageing, including impaired autophagy/mitophagy, senescence, and stem cell exhaustion, contribute to WS. They work closely with the WS patients in Norway. Gudmundsrud is also an editor of the Norwegian Centre on Healthy Ageing (NO-Age, https://noage100.com/), and an assistant coordinator of the Norwegian Alzheimer's disease network (NO-AD, https://noage100.com/no-ad/).

Speaker: Rebecca Presterud (MD/Ph.D. student from Hilde Nilsen group)
Title: xxx

Abstract:

xxx.

Biography:

xxx

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