UNIVERSITY OF OSLO

Anders Jahre's Awards for Medical Research 2020 and 2021 – The Jahre Lectures

Thursday 4 November 2021 at 10:00-13:10 hrs. Professorboligen, Karl Johansgate 47

The lectures are open to everyone. Register at *uio.no/jahreprisen* before 28 October.

PROGRAMME:

10.00–10:30 Professor **Jiri Lukas**
Novo Nordisk Foundation Center for Protein Research, University of Copenhagen
Intrinsic limits of genome surveillance: A conceptual framework to understand cancer

10.30–11:00 Professor **Jiri Bartek**
Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm and Danish Cancer Society Research Center, Copenhagen
Understanding cell cycle control and genome (in)stability: From mechanisms to clinical trials

11.00–11.25 Researcher **Niklas Björkström**
Center for Infectious Medicine, Karolinska Institutet, Stockholm
Differentiation, tissue-residency, and recirculation patterns of human natural killer cells

11.25–12.15 **Lunch**

12.15–12.45 Professor **Poul Nissen**
DANDRITE, Nordic EMBL Partnership for Molecular Medicine
Institute of Molecular Biology and Genetics, Aarhus University
Molecular mechanisms of transport in and out of brain cells

12.45–13.10 Professor **Barbara van Loon**
Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim
Importance of responses to damaged DNA bases in cancer and neurodevelopmental disorders

Anders Jahre's Awards for Medical Research *honor research of outstanding quality in basic and clinical medicine. The prizes are awarded by the University of Oslo and are among the largest within Nordic biomedical research.*

Jiri Lukas

PHOTO: LIZETTE KABRÉ

Jiri Bartek

PHOTO: TOMAS BERTELSEN

Niklas Björkström

PHOTO: MARKUS MARCETIC

Abstracts 2020:

Intrinsic limits of genome surveillance: A conceptual framework to understand cancer

Professor Jiri Lukas

Oncogenic transformation can be viewed as an accelerated Darwinian evolution, whose aim is to endow cancer cells with a selective advantage to proliferate. Our research has been dedicated to deciphering the molecular complexity of this process at the level of signalling pathways that safeguard the integrity of human genome during the cell cycle. Our ultimate goal is to understand how malfunctions of these mechanisms fuel cancer progression and how to use this knowledge to pave new ways for diagnosis and treatment. I will focus on a conceptual framework that has guided us throughout this endeavour: Time and again, we see that genome caretakers that repair damaged DNA have formidable limitations, which are exploited by cancer cells to bypass natural anti-proliferation barriers. On concrete examples of proteins that shield vulnerable DNA intermediates and that coordinate the dynamics of DNA replication with cellular metabolism, I will illustrate how cancer cells 'hack' into genome surveillance to gain proliferative advantage. However, I will not stop at this 'dark side' of oncogenic transformation – I will demonstrate that cancer evolution is a trade-off, where the initial gains that allow cancer cells to proliferate almost always come at the cost of newly acquired vulnerabilities, which are shared by many tumour types and can be targeted to selectively eliminate them. I will place these findings to a broader context of where we envision the 'hottest' areas to identify new cancer addictions to limiting genome caretakers and how to transform these findings to exploit hitherto concealed cancer vulnerabilities.

Understanding cell cycle control and genome (in)stability: From mechanisms to clinical trials

Professor Jiri Bartek

Cell proliferation and genome integrity maintenance are fundamental biological processes the proper execution of which ensures organismal development and homeostasis. Malfunction of the cell cycle and/or genome surveillance mechanisms can lead to developmental defects, premature aging and life-threatening pathologies including cancer, immunodeficiency and neurodegeneration, grave diseases and major societal challenges facing the mankind. We have primarily focused on gaining basic mechanistic insights into mammalian cell cycle control and genome integrity maintenance, as well as identification and exploitation of aberrations in these pathways in human diseases, particularly cancer. On several occasions, our basic discoveries paved the way to new concepts in cell biology and pathology, while our translationally oriented work provided candidate targets and biomarkers for cancer treatment, culminating in our recent drug repurposing efforts that have inspired several ongoing clinical trials in oncology. The lecture will present some of the conceptual advances we made, and provide examples of mechanisms and their relevance for understanding and management of cancer. From our cell cycle studies, the early elucidation of the cyclin D/CDK-p16ink4-pRB-E2F pathway and its universal deregulation in cancer will be complemented by our recent discovery of AMBRA1 as the master regulator upstream of the two major parallel G1/S-phase transition pathways: the cyclin D/pRB and the Myc-driven axis. Apart from discoveries of some DNA damage checkpoints, our concept of oncogene-induced replication stress (RS) inspired a new field of pathobiology, and the paradigm of cancer addiction to RS-tolerance mechanisms which allow survival and proliferation of tumor cells at the expense of genomic instability.

Differentiation, tissue-residency, and recirculation patterns of human natural killer cells

Researcher Niklas Björkström

The immune system is present throughout the human body. It was previously believed that immune cells circulated between the blood stream and different peripheral organs continuously surveilling those for invading pathogens or transformed cancer cells. However, we have in recent years learnt from experimental model systems that many immune cells instead permanently reside in peripheral organs, so called tissue-resident immune cells. This lecture will discuss recent insights into recirculation patterns, differentiation, and tissue residency of human immune cells with a particular focus on natural killer cells. Understanding the basic principles behind regulation of immune cell tissue residency will with time give new insights into how our local immune system responds during infections and cancer and what goes wrong when chronic inflammation occurs.

Poul Nissen

PHOTO: LISBETH HEILESEN, AARHUS UNIVERSITY

Barbara Van Loon

PHOTO: THOR NIELSEN

Abstracts 2021:

Molecular mechanisms of transport in and out of brain cells

Professor Poul Nissen

Transport and signalling in and out of cells are of fundamental importance for cell function and how life interacts with the environment. This is very apparent in the brain, where neurons are extremely active in circuit processing, and glia cells and endothelial tissues constantly maintain and regulate the brain environment. We study these mechanisms from a detailed structural and mechanistic perspective and have our main focus on how membrane proteins define electrochemical gradients and solute transport of the brain and are affected, or can be targeted, in brain disorders.

We have studied in particular P-type ATPases such as Na+, K+-ATPases, Ca2+-ATPases and P4-ATPase lipid flippases, as well as Na+-dependent amino acid transporters such as the glycine transporter GlyT1. Membrane protein crystallography and now also single-particle cryo-EM are critical methods for these studies along with biochemistry, biophysics, bioinformatics, and increasingly also network modelling and single-molecule and cell imaging techniques.

Furthermore, we have initiated structural and mechanistic studies of higher-order organization in neuronal compartments such as axons and presynaptic terminals using cryo-electron tomography. Our long-term aim is to model brain processes at molecular level through atomic models of structure, dynamics and emergence.

Importance of responses to damaged DNA bases in cancer and neurodevelopmental disorders

Professor Barbara Van Loon

Several thousands of damaged DNA bases are generated every day in each cell of our body. These lesions are caused by exposure to agents present in our environment and through adverse impacts of cellular metabolism. Increased levels of damaged DNA bases are associated with frequent diseases, including cancers and brain disorders. Different enzymes and pathways cooperate to sanitize damaged DNA bases and to maintain genome integrity. Less is known to what degree failure to coordinate DNA base repair with other cellular processes affects human health. We recently provided novel mechanistic insight in the coordination of DNA base repair with fundamental processes such as gene expression and DNA synthesis. By identifying modulators of responses to DNA damaging agents in cancer cells, we yielded directions towards rationalized use of chemotherapeutical drugs. We also demonstrated that DNA damage responses are of key importance during brain development and are dysregulated in some of the most severe neurodevelopmental conditions.

The Anders Jahre prize is a great inspiration for my future research directed towards discovering multi-faced functions of DNA lesion-recognition enzymes. A deeper understanding of the physiological and pathological impact of such functions is of importance for further advancements in diagnostics and therapy.