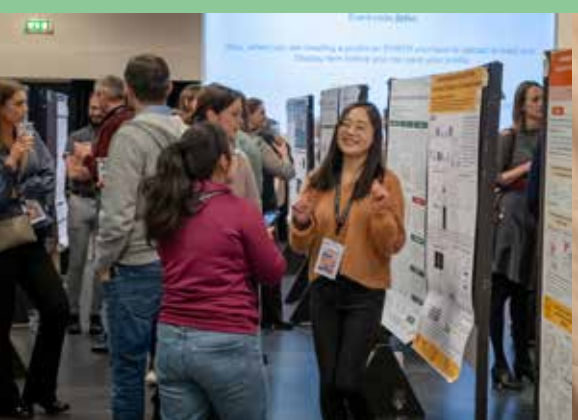
N:B:S Nytt

TIDSSKRIFT FOR NORSK BIOVITENSKAPELIG SELSKAP

Nr. 1 - 2024

59th NBS contact meeting 2024



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NBS-Nytt

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LAYOUT

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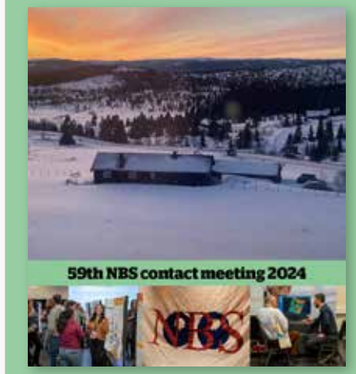

59th NBS contact meeting. Photos: Tone Berge, OsloMet and OUS, Nicola Montaldo, UiO, and Veronica F. Blihovde, NMBU.

s 6. NBS Bergen, Activities 2023

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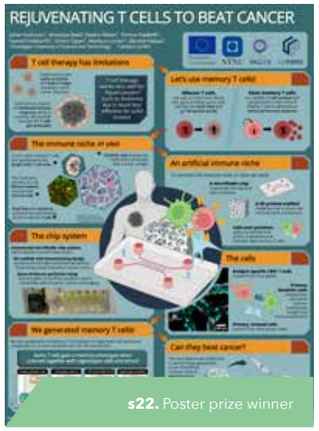


s22. Poster prize winner

s24. Biorabiaten

Veronica F. Blihovde
Redaktør

Ruth Tamara Montero
Redaktør

Dear readers of NBS-Nytt,
dear friends

In this edition of NBS Nytt, we welcome Rein Aasland as the new president of NBS. We will learn more about Rein and his career in the next editions and look forward to working together to further develop and improve NBS Nytt. We would also like to offer a warm thank you and our appreciation to Klara Stensvåg, the previous NBS president, for all the great work she has done for NBS and wish her all the best.

As we had the 59th NBS contact meeting earlier this year, we will have a summary of last years activities from the Bergen and Oslo local branches. Maybe some of the activites can spark inspiration and ideas for the other local branches for this year.

We then have the report from the NBS winter meeting and would like to thank the organising comitee for a wonderful meeting with great lectures, minisymposia, posters and exhibitors covering a wide range of fields in bioscience. We are also excited to congratulate two new Honorary Members of NBS, Kirsten Sandvik and Tore Skotland. Thank you for your inspiring and continued contributions to NBS. Further, we congratulate winners of the poster prizes and the best exhibitor stand during the winter meeting!

The NBS general assembly was also held during the contact meeting and in this edition you can read the minutes. An extra digital general assembly will be held at a later time to approve the accounts.

Further, you can read more about the interesting research of Janet Huisman, the winner of the popular vote poster prize at the winter meeting,

Biorabiaten intrigues us with his view on irisdiagnostics and how the eye can be a window into the state of health of various organs, both at present and in the future.

We also congratulate all new PhDs, this time we look at some from the University of Oslo and the University of Bergen.

Best wishes,
Veronica F. Blihovde and
Ruth Tamara Montero (editors)

Innleveringsfrister for NBS-Nytt 2024
Følgende innleveringsfrister er bestemt for kommende utgaver av NBS-Nytt.

NBS-Nytt nr.	Innleveringsfrister
1 - 2024	02/02/2024
2 - 2024	03/05/2024
3 - 2024	30/08/2024
4 - 2024	08/11/2024

Rein Aasland
President NBS

Dear Bioscientists,

It is a great honour to adress you as NBS' new president. I appreciate the trust I have been given and I shall do my very best to serve the Society during my term.

It is with great respect and gratitude that I take over the baton after Klara Stensvåg, who has served the Society excellently during the last five years; - one of the longest serving presidents in recent years. She chaired the Society through the pandemic and she has strived to keep the Society active and relevant. Importantly, Klara also led us through the discussions and deliberations that led to our name change to the Norwegian Bioscience Society.

We are just back from the 59th NBS Contact Meeting at Storefjell, perfectly organised by the Oslo team led by Anne Simonsen. We got an excellent set of plenary talks, both from foreign guests and from researchers in Norway. A wide range of topics was covered, including both new science and new technologies. One of the best and most interesting, I found, was the one by Pawel Burkhardt from the Michael Sars Centre in Bergen, who gave us remarkable new insight into the early evolution of nervous systems, revisiting more than 100 years old observations by Ramón y Cajal and Fridtjof Nansen and the then debate over the "neuron doctrine" and the competing idea of neuronal nets. The short talks in the parallel sessions were also of very high quality as were the posters. This year's meeting also had a large number of exhibitors presenting the latest developments and a couple of entirely new technologies. In fact, more than 30% of the meeting attendees came from the companies and providers.

My warmest congratulations goes to NBS' two new Honorary Members: Kirsten Sandvik and Tore Skotland, who were celebrated at the Meeting. Both have had long careers in Bioscientific research and served as excellent ambassadors for NBS and been very active participants and contributors to NBS meetings and other events over many years, both in the local Chapter and the National Society. The two new Honorary Members will be presented in the next issue.

As we sat down for dinner Friday evening, the news spread that our Minister of Research and Higher Education, Sandra Borch, had resigned following the disturbing news earlier in the day that her master thesis had been found to contain extensive plagiarism. As the Government is taking a student to Supreme Court for self-plagiarism, something most see as a much lesser breach of citation rules, Borch's position as Minister became untenable. This gave way to the Government's third leader of this Ministry, Oddmund L. Hoel, the first one since long who has solid experience from the sector. This gives hopes for a good and fruitful dialogue between the Ministry and the sector. During Saturday, news spread that also Minister of Health and Care Services, Ingvild Kjerkol's thesis contains plagiarism. This thesis is currently under scrutiny by the Nord University. These two stories reminds us on the importance of training our students proper citation and crediting other's work. The new draft law for Universities and Higher Educaton will strengthen the sanctions for plagiarism. But what we really need is, as proposed by law professor Johan Giertsen (Bergen) ; a clear definition of what cheating is, much like the current law for Research Ethics. And, I rush to add, a much wider set of responses and sanctions suitable for lesser breaches. This will allow for a better climate for training and management of the rules and culture for proper citation in science. But one thing must be clear: cheating is cheating, and plagiarism is theft, however small it is.

But I guess that many of you are even more concerned about the current financial situation for research in Norway, both per core funding of universities and research institutions, and funds made available to the Research Council (RCN). In times when societal challenges are mounting, with needs to find new solutions for e.g. better health, biodiversity, and food production and safety, increased investments in bioscience research seems obvious, and in particular, long term financing for fundamental research. Can NBS make a difference in the public debate on such topics?

Allow me to recall, anectdotally, a story from the past: In 2010, we were in the last lag of RCN's FUGE ›

program, a 1,6 bn NOK program over ten years to boost technology platforms for Norwegian bioscience. Both the Ministry and the RCN were discussing what do do next, including plans for a new program for biotehnology. At that year's NBS Contact Meeting at Storefjell, many of us contacted and discussed the situation and were concerned about future funding and how it would be designed and implemented. An interesting idea emerged: *what if the University Rektors mounted a joint effort?* But how could that come about? Who could approach them and draft a unified proposal? Professor Odd Stokke-Gabrielsen's name soon came up and I offered to call him there and then. Odd agreed and this resulted in a proposal to the RCN signed by six Rektors. Although we do not know the details, there are reasons to believe that this letter contributed to the formulation of the BIOTEK2021 programme launched in 2012, and within this, the "*program-within-the-program*" Digital Life Norway launched two years later.

The NBS Contact meeting is a unique venue for many types of contacts, such as young scientists seeking new labs or advice on going abroad, foreign scientists wishing to learn about bioscience activities in Norway, and more. Activities in NBS' regional chapters are also an essential part of NBS. With this in mind and more, we should consider how to make NBS more relevant to the Norwegian bioscience community in the time to come.

Best reguards,
Rein

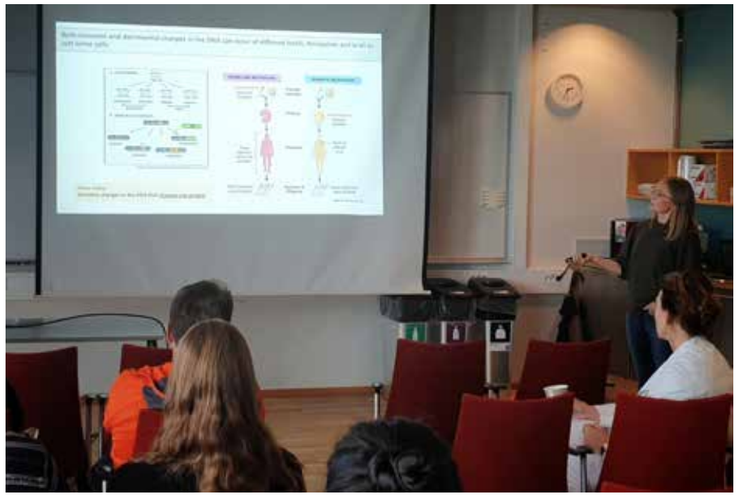
1. See Khrono, Jan 23rd, 2024 - https://www.khrono.no/jussprofessor-advarer-stortinget-mot-nye-fuskeregler/843498

NBS Bergen

Activities 2023

In 2023, NBS Bergen arranged three seminars under the heading "NBS Science and Social", where scientific meetings were combined with social activities such as board games, payday beers or other fun activitites like a game of curling.

In the first "S&S" event of 2023, Tim P. Lynagh from the Michael Sars Centre delivered a talk titled "Neurotransmitter Receptors Mediate Rapid Signals Between Cells by Coupling Ligand-Binding to Electrical Currents." In September, former NBS Bergen leader Marte I. Flydal from the Medical Genetics Department at Haukeland University Hospital returned to our stage and talked about her current work and research. Her talk, titled "Interpreting Spelling Errors in DNA: Innocent or Detrimental?" provided insights into the life of a molecular biologist with responsibility for interpreting potential disease-causing variants identified by exome sequencing of patients. Later that evening, we celebrated her talk with a crash-course followed by a prestigious game of curling at the ice rink.



Despite some participants waking up with rainbow-colored buttocks the next morning, it was a lot of fun! Luckily no arms or bones were broken. Finally, we held our annual Christmas meeting and general assembly featuring a talk from Karl Johan Tronstad titled “Metabolic Phenotypes: Key Indicators of Health and Disease”. It was an interesting talk where Karl Johan presented some of the groundbreaking work they currently are doing on Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Following the scientific talk, NBS members enjoyed a Christmas beer tasting led by the former NBS Bergen general, Rune Kleppe. His passion for strong, dark Christmas beer made the Christmas meeting a great success, and we already asked Rune for a follow up in December 2024.

In 2023 the NBS Bergen board consisted of Svein Isungset Støve (Chairman), Rasmus Moen Ree (Deputy Chairman), Anita-Elin Fedøy (Treasurer), Andreas Midlang (NBS-Nytt Contact Person) and Marc Niere, Kunwar Jung-KC, Thomas Stevenson, Solveig Siqveland and Mary Dayne Sia Tai (Board Members). At the general assembly, all members of the board were elected for a new period, and two new members, Valeria Kalienkova and Alessia Caiella, joined as board members. The NBS Bergen Board is looking foreward to 2024, were we aim to continue with NBS Science and Social seminars, as well as arranging a spring and an autumn NBS symposium with talks from young local researchers and a poster session. We hope that many of our members will attend!

NBS Oslo

Summary of activities for 2023

In 2023, NBS Oslo hosted two captivating events that enriched our scientific community.

Unfortunately, we bid farewell to our former NBS Oslo board president, Deo Pandei, as well as board members Pooja Kumari and Marco Pannone.

We kicked off the year with the 3rd Oslo Science Life-Story featuring Professor Anne-Lise Børresen-Dale on March 16th. Prof. Børresen-Dale, a distinguished figure in molecular tumor biology, shared profound insights into her groundbreaking contributions to breast cancer research. Her lecture inspired attendees with pioneering discoveries and contributions to the field, shaping the landscape of life sciences and advancing our understanding of cancer biology.

Later in the year, on September 7th, we hosted an insightful NBS talk featuring Mika Gustafsson, Professor in Translational Bioinformatics at the University of Linköping, Sweden. His presentation titled "Deep learning using omics repositories for identification of disease risk factors and genes" captivated the audience, attracting approximately 35 students and scientists.

Since our general assembly last spring, our board has comprised Nicola Pietro Montaldo (president), Tone Berge (NBS board representative), Arja Katrina Lea Arnesen Løchen (treasurer), and Erwan Delabarre (board member).

Looking ahead, our next general assembly is scheduled for February 8th, 2024, coinciding with our Winter Poster Meeting. This event aims to foster connections and encourage collaborations among scientists in the Oslo area. We are excited to host Senior Scientist Helga Bjarnason Landsverk (OUS), who will enlighten us with her research topic: "DNA damage response and transcription."

Let's continue our journey of discovery and collaboration in 2024

Nicola Pietro Montaldo

The board. From left to right: Nicola Pietro Montaldo, Tone Berge, Deo Pandei, Marco Pannone, Aria Løchen

Prof. Anne-Lise Borresen-Dale, University of Oslo

Prof. Mika Gustafsson, University of Linköping

NBS Winter meeting 2023

The 59th NBS contact meeting was held at Storefjell Moutain Resort Hotel at Gol in January. The program which was well-organised and compact, included distinguished national and international speakers from several bioscientific fields, three parallel minisymposia sessions, two poster presentations and numerous relevant exhibitors from all fields of life science. There was also set aside time for outdoor activities like skiing, sledding and walks, before the winter meeting concluded with the NBS general assembly and a banquet dinner.

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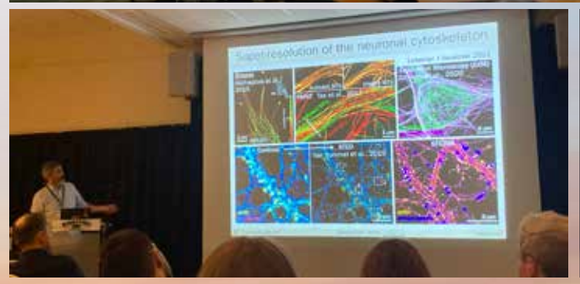
Institutt for husdyr- og akvakulturvitenskap,
Fakultetet for biovitenskap,
NMBU

Photos: Tone Berge, OsloMet and Oslo University Hospital (OUS), Nicola Montaldo, University of Oslo (UiO) and Veronica F. Blihovde, Norwegian University of Life Sciences (NMBU).



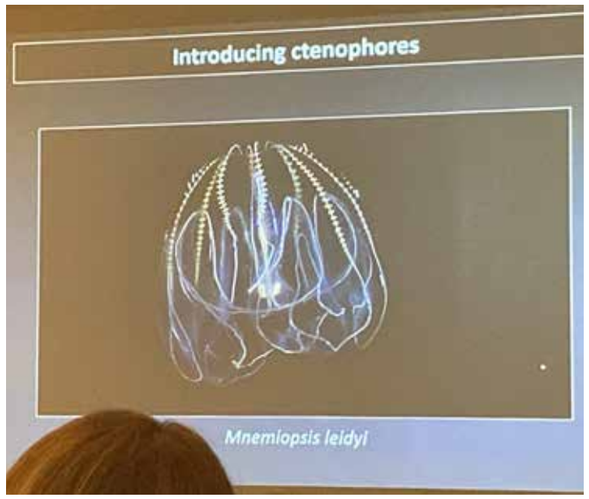
Opening of the meeting and Thursday afternoon plenary lectures

Just a day after one of the snowiest days Oslo has seen in years, we got on the bus from the Oslo bus terminal to Storefjell Resort Hotel in Gol. The 3-hour bus ride in -12°C and sunshine, took us through beautiful winter wonderlands and up the mountain to the hotel. After check-in, we received our name badges and a NBS tote bag containing some brochures from some of the exhibitors at the contact meeting. As the posters were being hung up ready for the first poster session, which would already be later this day, the meeting program began with lunch in the restaurant with a panoramic view of the picturesque surroundings. The lunches and dinners consisted of a buffet allowing people to enjoy a variety of Christmas food as well as a selection of other dishes while socializing with both newly formed and old contacts.

The scientific program was initiated with a warm welcome from Anne Gjøen Simonsen, the committee chair of the meeting, who thanked sponsors and vendors before introducing the speaker of the first plenary lecture of the contact meeting. This lecture, which was sponsored by The Centre for Cancer Cell Reprogramming, was held by **Mariano Barbacid** and entitled ***"Past and future of precision medicine in cancer".*** Professor Barbacid is a group leader at the Spanish National Cancer Research Center (CNIO), in Madrid, Spain. In 1982, his work led to the isolation of the first human oncogene, HRAS and the identification of the first mutation associated with the development of human cancer. Later, Professor Barbacid has been credited with the isolation of the TRK oncogene from a colon carcinoma, identification of the TRK family of tyrosine protein kinase receptors as the functional receptors for the nerve growth factor (NGF) family of neurotrophins and has pioneered the development of "targeted therapies". His work has been recognized by several domestic and international awards, successfully securing two ERC Advanced Grants and over 300 published papers. Now, his work focuses on identifying therapeutic strategies against KRAS mutant tumours, a mutation that accounts for more than 20 % of all human cancers.

During his plenary lecture, professor Barbacid talked about how the term "cancer" refers to more than 150 different diseases but is still used in singular form in many languages. Their only common ability is to proliferate in a disorganised manner and colonise other tissues and organs. The heterogeneity of different types of cancer however, is based on several parameters, such as organ, cell of origin, driver mutations, tumour microenvironment, tumour heterogeneity, tumour grade and metastatic growth. Professor Barbacid then discussed the development of cancer treatment strategies over the years, from chemotherapy and photonic radiotherapy to precision medicine, immunotherapy and CAR-T cells. He then concludes by highlighting the importance of hospitals always sequencing for druggable oncogenes to improve cancer treatment for the patients.

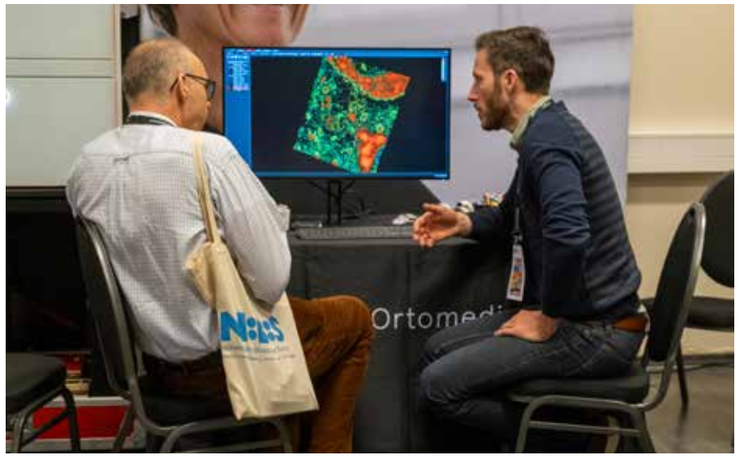
The second plenary lecture, entitled ***"Open technologies in the quest for nanoscale live-cell imaging"*** was held by **Ricardo Henriques** and chaired by Kay O. Schink. Professor Henriques is a group leader at Institute Gulbenkian de Ciência in Oeiras, Portugal, moving his laboratory in 2020 from University College London and Francis Crick Institute in the UK. Professor Henriques has made significant contributions to the fields of cell biology, computational imaging and super-resolution microscopy through pioneering innovative technologies, methodologies and knowledge. With a background in biophysics, specializing in biophotonics and robotics, his group uses optical and computational biophysics to study cell biology and host-pathogen interactions. Professor Henriques' technological developments are distributed throughout the Cell Biology and Biomedical research community. His algorithms QuickPALM, NanoJ, SRRF and SQUIRREL are among the most used and ›



cited analytical methods in the Super-Resolution Microscopy field. His core philosophy has been to make his research reproducible, transparent and open-source.

During his talk, professor Henriques explains that super resolution gives us the possibility to see the mechanism of the structures we can see with electron microscopy imaging. He talks about the use of deep learning in microscopy and how the use of a trained deep learning algorithm could be used to predict a microscopy image with for instance decreased noise or improved resolution. He also specifies that even though technologies like this can improve the quality of microscopy images, it is important to consider when one needs real data and when it's possible to use a predicted image. His final take-away is that one should always cross reference with a different method.

The next plenary lecture, chaired by Harald Stenmark, was the 2024 FEBS National Lecture which was held by **Graça Raposo** and entitled "***Watching the cell from inside to outside: Lysosomes, Extracellular Vesicles and Friends".*** Professor Raposo is Research Director at CNRS (National Centre for Scientific Research) and Team leader at Department of Cell Biology and Cancer at Institute Curie in Paris, France. Raposo is one of the pioneers and world's leaders in understanding the cellular and molecular principles underlying the biogenesis and functions of extracellular vesicles, exosomes, microvesicles and lysosome related organelles. Professor Raposo's research focus has been on how the process is regulated at the cellular and tissue level from fundamental mechanisms to applied research. Her work has made influential contributions in the fields of immunology and cancer, neurodegenerative diseases and skin pigmentation. Raposo's studies lead to development of therapeutical strategies in cancer and pigmentation, and she is an internationally renowned expert in state-of-the-art imaging and electron microscopy.



In her lecture, professor Raposo talks about how the endosomal system is a network of organelles with important roles for physiological processes, such as nutrient uptake, macromolecule degradation and signalling in eukaryotic cells. The existence of specialised cell types of organelles which share features with lysosomes so called lysosome-related organelles (LROs) highlights specialisation of the endocytic pathway. The melanosome, which is the pigment granule produced by skin melanocytes, is a model LRO. Additionally, the secretory capacity of multivesicular endosomes (MVEs) and the subsequent release of their intraluminal vesicles into the extracellular space, called exosomes, is another functional modulation of the endosomal system. Exosomes and ectosomes, which are released from the plasma membrane, carry proteins and genetic material making them imperative in cell-to-cell communication in health and disease. They use state of the art imaging methods with biochemistry and molecular biology to answer their projects research questions in these topics.

Exhibitions and poster sessions

Numerous exhibitions from very well-known companies such as Eppendorf, Thermo Fisher, Avantor/VWR, Bio-Rad, Qiagen, Sarstedt and BioNordika, as well as several others, presented materials and services on their stands. With such an excellent turnout of highly relevant exhibitors, its good the program consisted of several sessions to ensure there was enough time to see and meet them all. Many also had competitions where you could guess the number of tips or tubes in a bottle, spin the wheel or throw ping pong balls into cups to win anything from a notebook, cup or even up to 3 hours use of a core facility. During the last exhibition session, the exhibitor prize for best stand was awarded to Bio-Rad.

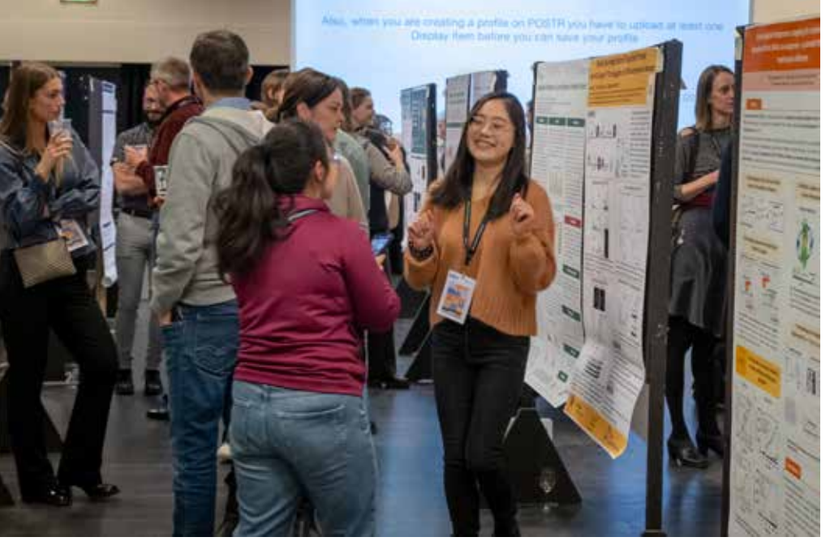
In the same area as the exhibitions, the winter meeting included two poster sessions, with the first one taking place already on the first day. Among the 49 posters, a wide variety of research fields were presented, including, but by no means limited to topics within cancer, immunology, aquaculture, DNA methylation, epigenetics and bioinformatics. This provided a great opportunity to meet and discuss exciting research with both young and established researchers early in the meeting which also facilitated further communications throughout the meeting. The poster prizes, which were awarded during the banquet Saturday evening and who's winners will be presented later in this text, were sponsored by the computational and structural biotechnology journal.

Friday plenary lectures

The first session on Friday was chaired by Pål Selbo and the plenary lecture ***"Personalised immunotherapy for treatment refractory metastatic breast cancer"***.

was given by **Jon Amund Kyte**. Dr. Kyte is head of the Department for Clinical Cancer Research and a research group leader for "Immunotherapy against solid cancers" at Department for Cancer Immunology, Institute of Cancer Research both at Oslo University Hospital. In addition, he is a Professor in Clinical Research at Oslo Metropolitan University. Having a background as both a clinical oncologist and immunotherapy researcher with experience as a consultant in breast cancer and at the Early Phase Trial Unit, Dr. Kyte has initiated and conducted several clinical trials combining immunological checkpoint inhibitors with chemotherapy or radiotherapy. Based on material from immunotherapy trial the Kyte research group aims to personalize cancer immunotherapy and develops tumour-targeting chimeric antigen receptors (CARs) for T cell therapy against solid cancers, as well as strategies designed to make the CAR T cells resistant to immune suppression.

During his talk, Dr Kyte explains that although immunotherapy has shown important progress in cancer treatment, the use of immune checkpoint inhibitors (ICI) mainly only show efficacy in cancers with existing immune responses and only rarely in "immune-cold" tumours such as those of metastatic breast cancer (mBC), where only a minority of patients respond to ICI. Being among the most common causes of cancer-related death worldwide, there is a strong need for biomarkers and improved treatment strategies for mBC. In this regard, they have conducted two randomized trials, called ALICE and ICON, evaluating the addition of ICI to selected chemotherapy with immunomodulating properties. Being the first to evaluate ICI combined with anthracyclines, which stimulates immunogenic cell death, and metronomic



cyclophosphamide, which counters immunosuppressive regulatory T cells, in metastatic breast cancer, the ALICE trial targeted triple negative mBC and the ICON trial targeted hormone receptor positive mBC. Supporting the use of selected chemotherapy to make "immune-cold" tumours responsive to ICI, the ALICE trial is the first to show benefit from adding ICI to chemotherapy in PD-L1negative mBC. The ICON trial showed no benefit from concomitant addition of ICI to chemotherapy but did display responses from ICI after chemotherapy. The fraction of regulatory T cells was reduced by the selected chemotherapies in both trials. Using extensive biobank material collected from the trial patients, the Kyte research group are currently conducting translational projects investigating biomarkers, mechanisms of effect and of tumour escape. Providing information for new clinical trials and insight into immune-tumour co-evolution these studies will hopefully benefit development of improved and personalised therapy for hard-to-treat cancers.

The next two sessions were chaired by Trine B. Haugen and the first plenary lectures of these was held by **Trude H. Flo** with a talk entitled "***Spatiotemporal studies of host responses to mycobacteria in macrophages".*** Professor Flo is the Director of the Centre for Molecular Inflammation Research at the Norwegian University of Science and Technology (NTNU) in Trondheim. Focusing on understanding host responses to mycobacteria and viruses and virulence strategies employed by these pathogens to parasitize host cells, her research interest has long been innate immunity. The approach to use microscopy combined with molecular techniques to spatiotemporal dissect host-pathogen interactions has provided new knowledge about pathogen recognition, inflammatory signalling and cell death. Such as the group's recent discovery that a potentially promising new HIV therapy could be Toll-like receptor 8 (TLR8) ligands as HIV is detected by TLR8 in T cells. To investigate how mycobacteria are sensed as they move within immune cells, they have utilized microscopy techniques such as time-lapse and correlative light- and 3D electron microscopy (CLEM). The first image of inflammosomes in situ in M-tuberculosis-infected macrophages were taken by the Flo group using CLEM.

During her lecture, Professor Flo talks about tuberculosis, caused by Mycobacterium tuberculosis (Mtb), which is among the leading causes of death overall and the second cause of death from infection. Infection occurs by inhalation into the human lung and macrophages are the first cells to be infected. Some of these macrophages undergo cell death by various mechanisms, such as necrosis, pyroptosis and apoptosis. It has been suggested that during infection the host or bacterium differentially benefit from different modes of cell death. Professor Flo's research group investigates how bacterial survival and inflammation is affected by cell death and the mechanisms behind them involved in Mtb-induced infection. In order to study the intracellular communication and cell death during Mtb infection, the Flo research group have used induced pluripotent stem cell (iPSC)-derived macrophages and gas-exchanging alveolar epithelial cells type 2 (AT2s) to establish a tractable lung-mimetic co-culture model.

The following plenary lecture was held by **Pål Falnes**, entitled ***"The bioscience (biochemistry and biology) of protein methylation"***. Professor Falnes leads the Biological methylation research group, which is a part of the Centre of Excellence CRESCO (Centre for Embryology and Healthy Development, at the Department of Biosciences at the University of Oslo. Modification of the cellular macromolecules RNA, DNA and proteins are numerous, including modifications such as methylation and hydroxylation which can give epigenetic modifications of DNA and chromatin proteins which have regulatory roles. Identifying novel human enzymes involved in the introduction and removal of such modifications is the main research interest of the Falnes group. Utilizing both biochemical characterization of the modification enzymes and analysis of the modifications in a cellular or organismal context, they also investigate the biological significance of the respective modifications.

In his lecture, Professor Falnes talks about post-translational methylation, mainly occurring on lysines and arginines, which is mediated by highly specific methyltranserase (Mtase) enzymes. Regulation of chromatin packaging and gene expression, caused by specific methylations of the flexible N-terminal tails of histone proteins, has been the main study area of protein methylation. An important step towards investigating the molecular and biological function of methylations occurring on non-histone proteins has recently been made with the identification of a number of novel protein MTases targeting non-histone proteins. The Falnes research group has during the last years discovered a number of novel human lysine specific MTases. Methylation by these lysin specific MTases typically occurs on a single, highly abundant protein with an essential cellular function, which usually belongs to protein groups such as molecular chaperones, mitochondrial proteins and components of the protein synthesis machinery. Even though the knowledge that some mammalian proteins are methylated on histidine has been known for more than 50 years, it was only in 2018 that the first corresponding histidine-specific Mtase (HMT) was identified. Furthermore, the Falnes research group has since discovered and characterised two novel human HMTs.

The next plenary lecture was a Dentist Olaf Aase and wife memorial lecture and chaired by Erik Boye. The lecture was given by **Susan Gasser** and entitled ***"Responding to DNA damage: how to cope with stress".*** Professor Susan Gasser is Director of the ISREC Foundation for Cancer Research in Lausanne in Switzerland. With a background in biophysics, biochemistry and more specifically in mitotic chromosome structure, chromatin organisation and replication, Professor Gasser became a professor of molecular biology at the University of Geneva in 2001. She then moved to Basel as a professor at the University of Basel and Director of the Friedrich Miescher Institute for Biomedical Research from 2004-2020. Professor Gasser's research laboratory uses both budding yeast and the nematode C. elegans to investigate heritable gene expression and the functional impact of the spatial packaging of interphase chromatin has on this. This includes specifically focusing on the identification of factors that spatially segregate large chromatin domains, dynamic changes in chromatin during DNA repair and stress-induced epigenetic function. Professor Gasser was elected to the Académie de France, EMBO, Leopoldina, the Swiss Academy of Medical Sciences, has received prestigious awards, holds two honorary doctorates and has authored more than 300 articles.

Professor Gasser's lecture consisted of three parts, where in the first two parts she talks about the importance of quantification of research results, refers to the quote "*The book of nature is written in the language of mathematics*" by Galileo Galilei and how this is key to their research approach. The Gasser research group has studied the localisation and dynamics of specific chromosomal loci in vivo by live imaging microscopy. In order to maintain genome integrity and proper chromatin organisation, nucleosomes are essential in eukaryotes. At the site of a DNA break histones are however often removed and repair factors are recruited to the break site. The Gasser research group showed that a response to DNA damage checkpoint response is a drop in total levels of core histones and that this in addition to degradation of histones, depends on the chromatin remodeler complex INO80 and the proteasome. Professor Gasser explains that her group was able to quantify changes in the chromatin-associated proteome upon zeocin-induced DNA damage using a quantitative mass spectrometry-based approach. This identified a 20-40% loss of core histones, a substantial reduction of RNA polymerases and most nucleosome remodelers. In the third and last part of

Professor Gasser's talk, she gives the following 7 lessons in how to be a great scientist and suggest that these are guidelines on how to have a stress-free science career.

1. Quantify, quantify, quantify. cannot argue with numbers.
2. Embrace new technologies - always (Sidney Brenner).
3. Be creative (be brave) (Gascoyne) (Sydney Brenner).
4. Do what you are passionate about (despite obstacles).
5. Be flexible. Take the big view (step back, regroup but keep going).
6. Be generous, let others develop.
7. Remember - science -in the end - is about people.

And have fun!

We continue with the only digital talk of this winter meeting, in a session chaired by Helene Knævelsrud, this plenary lecture held by **Christine Mayr** was entitled ***"How the location of protein synthesis controls protein function"***. Professor Mayr is a professor at the Gerstner Sloan Kettering Graduate School of Biomedical Science and at the Weill Cornell Medical College in New York, USA. She holds a M.D. and a PhD in immunology from Berlin, Germany and her postdoc, in David Bartel's group, led her to the finding that oncogenes can get activated through 3'UTR shortening. Professor Mayr started her own laboratory in 2009 the Cancer Biology and Genetics Program of Memorial Sloan Kettering Cancer Center in New York. She was awarded the NIH Director's Pioneer Award in 2016, to continue her study of mRNAs with functions beyond their roles as templates for protein synthesis and further elucidation of protein-protein interactions which can regulate protein function through 3'UTRs. The Mayr lab identified two cytoplasmic membraneless compartments, the "TIS granule network" and the "FXR1 network" and now focuses on investigating how protein conformation and activity can be changed by translation in these mRNA-based compartments. Furthermore, they found that specific functional classes of proteins are translated in particular cytoplasmic neighbourhoods. Together, these results strongly suggests that protein conformation and protein function is affected by the location of protein synthesis.

In her talk, professor Mayr talked about their recent finding that there is not a uniform distribution of mRNAs encoding non-membrane proteins across the cytoplasm. In addition to the well-known components of the cytoplasm, the soluble cytocol and lipid-membrane-enclosed organelles, the cytoplasm also contains mRNAprotein networks such as TIS granules and the FXR1 network. The functional classes of encoded proteins greatly differ in subcytoplasmic mRNA localisation, for instance mRNAs encoding transcription factors, such as MYC, are strongly overrepresented among TIS granuleenriched mRNAs. Professor Mayr's research group then further examined whether the location of mRNA translation would have an effect on the function of MYC. They found that the function of MYC differed depending on whether the mRNA was translated in the TIS-granule or in the cytosol and that this difference was caused by mRNA-dependent MYC protein complexes that can only form upon translation of MYC in TIS granules. The future use of RNA targeting to control transcription factor function, requires a better understanding of mRNA dependent transcription factor complex assembly.

Minisymposia

A total of nine minisymposia were held with three parallel sessions at a time, with each of the 53 talks having 15 minutes to present. The first session had the topics diseases/therapy, DNA/chromosomes and cell biology 1. More specifically these talks focused on areas of research within molecular pathways in cancers, biomarkers, cell cycle phases, organisation of chromosomes, mitophagy and autophagy. The second session included the topics biochemistry/methods, microbiology/enzymology and immunology. In this session, the topics specifically included research about mitochondria, genomics, salmon microbiota, electron transport, macrophages and HIV. The third session covered the topics biochemistry/genetics, methods and cell biology 2. In more detail, this part covered fields within hypoxia, protein localisation, cytotoxicity, DNA and RNA isolation, marine microalgal pigments and stress granules. This broad variation offered something of interest for everyone and sometimes more than one interesting talk at a time, meaning there was a good turnout for all the talks.

Saturday outdoor activities and plenary lectures

Saturday morning was set aside for outdoor activities with several available options. The location of the hotel, in the middle of Storefjell mountain, gives the perfect opportunity to go cross-country or downhill skiing, sledding or for a walk up the mountain. Although very cold, with temperatures close to -20 °C, the weather this day provided nice conditions for all the above-mentioned activities and a beautiful, clear view from the mountain top.

The plenary talks of the day were held in the late afternoon, after a minisymposia session with the first chaired by Tone Berge. The lecture titled "***Evolutionary origin(s) of synapses and neurons***" held by **Pawel Burkhardt**. Dr. Burkhardt is a research group leader at the Michael Sars Centre in Bergen, Norway and his research focuses on using marine organisms to understand the molecular and cellular mechanisms that underlie the origin of synapses and neurons. He has a background in biology and worked on rat and choanoflagellate (neuro-) secretory proteins and choanoflagellate postsynaptic protein homologs during his Master, PhD and postdoc. In 2018, Dr. Burkhardt started his own research group ""Evolutionary Origin of Synapses and Neurons" at the Sars Centre and in 2022 he was awarded an ERC consolidator grant.

In his lecture, Dr. Burkhardt talks about two main parts, "The ancestry of the synaptic toolkit" and "The appearance of the first neuron". Neurons communicating through synapses is the hallmark of a nervous system, but the evolutionary origin of nervous systems, remains an important question in biology. In comparative studies into the evolutionary origin(s) of neurons and their connections, marine organisms ›

both with and without nervous systems play a key role. On the path to elucidating the origin of the first neuronal circuits, Dr. Burkhardt enthusiastically describes results from his group on fast calcium signalling in a neuron-less organism. In the second part of his talk, "The appearance of the first neuron", Dr. Burkhardt explains that there are two main hypotheses of which was the first animal, the sponge-first or ctenophore-first hypothesis. For their investigations, they have established a culture system for the ctenophore Mnemiopsis leidyi at the Sars Centre. This model organism can also be collected from the sea, at depths of 700 m and reaches its larva stage within 24h. Their whole bodies are covered by a nerve net and until very recently, not a single marker for the ctenophores nervous system was known. A focus of Dr. Burkhardt's research has been how the ctenophore neurons are connected as they do not have synapses. Although there are other synapses, for instance to effector cells, in ctenophores, there are none in the nerve net. Using high-resolution three-dimensional electron microscopy, Dr. Burkhardt's research group has shown that neurons of the ctenophore nerve net are interconnected through continuous neurite plasma membranes without evidence of synapses, comprising a single neuronal circuit rather than being separate entities. These results present a new view on neuronal network organisation and neurotransmission in ctenophores and thoughts of the first neuron.

Chaired by Pooja Kumari, the last plenary lecture of the NBS winter meeting was a Nikon sponsored talk and held by **Christophe Leterrier,** entitled ***"The functional nano-architecture of axonal actin".*** Dr. Leterrier main focus of study is how neurons are organised at the cellular level. His background as an engineer, then in cell biology and neurobiology led him to his position as a team leader of the NeuroCyto lab at the Neuropathophysiology Institute in Marseille, France. To investigate how molecular assemblies organise the neuron and forms their physiology, Dr. Leterrier's group utilise advanced microscopy techniques to directly observe them at the nanoscale.

During his lecture, Dr. Leterrier talks about how axons must continuously adapt to changes in the environment and that the cytoskeletal organisation takes part in the coordinated transport, anchoring and assembly of axonal components. To investigate the nanoscale architecture of cytoskeletal and scaffold structures within the axon, the Leterrier lab uses super resolution microscopy. This allows them to look at presynaptic actin assemblies and clathrin-coated structures among other things. Using a combination of labelling approaches, correlative live-cell/super resolution/electron microscopy (EM) and quantitative analysis they can study the molecular organisation and functions of the axonal architecture at a nanoscale. The Leterrier research group used the super resolution imaging technique 3D-STORM to follow a spectrin-labelled axon. They were able to take the top part of a cell off, unroofing a neuron, which makes the periodic scaffold visible. This allowed them to see that spectrin connects to the actin rings and obtain the first EM visualization of actin rings. Further they saw clathrin pits in holes of the spectrin scaffold, also after unroofing the neurons, and are working on further investigations of these findings.

NBS general assembly and banquet

Minutes from the NBS general assembly can be read elsewhere in this edition. As revision of the account had not been done by the time of this meeting, an extraordinary GA to vote on approval of the accounts will be held digitally later. The banquet held later that evening, consisted of good food, engaging conversations between old and new colleagues, collaborators and friends, in addition to engaging speeches. During the evening, three poster prizes were awarded, one which was selected by popular vote through the app Postr and two which were selected by a poster commitiee. The winner of the best poster selected by popular vote was Janet Huisman, a PhD candidate at the Norwegian University of Science and Technology in Trondheim, with the poster "*Rejuvenating T cells to Beat Cancer Using Artificial Immune Niches*". You can read more about her interesting research elsewhere in this edition. The poster prizes selected by a poster commitiee was awarded to Thea Josefine Christensen, a research associate at Oslo University Hospital and University of Oslo with a poster entitled "*Development of ex-vivo 3D culture assay to facilitate preclinical testing of B-cell non-Hodgkin´s lymphoma*" and Katharina Vestre, a postdoc at the University of Oslo and Oslo University Hospital, with the poster "*Cell Biology of Cancer Cachexia*". Congratulations to all!

Further, two new Honorary Members of NBS were presented. Kirsten Sandvik and Tore Skotland who both have had inspiring scientific careers as well as longstanding and active roles in NBS. The Department of Core Facilities at Oslo University Hospital, running seven regional core facilities and led by Leonardo A. Meza-Zepeda, awarded various hours at a core facility of choice to winners of the competition held during the exhibition sessions earlier in the meeting. Speeches of appreciation were held for the general secretary, Magnus Steigedal, and the previous NBS president Klara Stensvåg for their dedication and continued work for NBS. We then took part in the ceremonial handing over of the gavel from the previous NBS president Klara Stensvåg to the new president of NBS, Rein Aasland. Finally, several speeches also thanked the organising committee for organising such an inspiring and well planned NBS winter meeting. The evening was concluded with live music by the band "Free Fruits" and later with music from plenary speaker and DJ Christophe Leterrier.

Take away

In my opinion, the best experience of the NBS contact meeting is the low threshold to talk to anyone, no matter position, experience or any other classifier. Everyone is passionate about bioscience, interested in research and open to making new contacts. Thank you to the organisers, presenters, exhibitors, sponsors, participants and everyone involved for making this a very successful and interesting contact meeting! We look forward to the 60th NBS contact meeting next year which will be organized by NBS Bergen and held in Røros.

General Assembly of the Norwegian Bioscience Society **Meeting Minutes**

Time: Saturday 20. January 2024
Place: Storefjell Høyfjellshotell, 3550 Gol i Hallingdal

Agenda

A. Opening of the general assembly (President).
B. Approval of the invitation and agenda.
C. Election of chairperson, 2 minutes secretaries and 2 persons to approve that the report for the general assembly is correct.
D. Approval of the board report.
E. Approval of the revised accounts of NBS, NBS-nytt and Contact Meeting 2022
F. Election of president and/or general secretary.
G. Matters proposed by the board:
H. Other matters received:
I. Approval of the proposed budget
Orientations
J. NBS-nytt: the editor informs about NBS Nytt 2023.
K. Report from NBS local branches.
- Oslo
- Bergen
- Trondheim
- Tromsø
- Ås

L. NBS Contact meeting 2025: Trondheim
M. NBS Contact meeting 2026: Bergen

Minutes:

A. Opening of the general assembly (President).

The President of NBS Klara Stensvåg opened the General Assembly

B. Approval of the invitation and agenda.

Approved

C. Election of chairperson, 2 minutes secretaries and 2 persons to approve that the report for the general assembly is correct.

The following people were elected:
Chair: Magnus Steigedal
Secretaries: Svein Isungset Støve and Veronica F. Blihovde
Approval: Nicola Pietro Montaldo and Torkild Visnes

D. Approval of the board report.

The board report was approved. A summary of the report is below:

Board report for 2023

Boardmembers

Klara Stensvåg has been the president for the whole period. Magnus Steigedal has been secretary general and has been doing the day-to-day activities in the society including follow up on the economy. The rest of the board has been Tone Berge (Oslo), Gustav Vaaje-Kolstad (Ås), Svein Isungset Støve (Bergen), Nadra Nilsen (Trondheim) og Ole Kristian Greiner Tollersrud (Tromsø). From December 2023 Sabina Leanti La Rosa is the new member of the board representing Ås. President elect Rein Aasland has also taken part in the board meetings.

Number of members

The NBS has around 250 members. Most members renew their membership in connection to the contact meeting.

NBS-Nytt

Veronica F. Blihovde has been the editor of NBS-nytt, and we also have a co-editor: Ruth Tamara Montero. In 2023 we have had the full digital transition that has led to a dramatic cost reduction in producing and distributing NBS-nytt. The magazine is now open to also non-members as suggested by the General assembly. We will continue to make NBS-nytt more visible to our scientific communities in 2024.

Accounting

Andromeda Økonomi with Irmelin Krogsæter has function as accountant for NBS.

Board meetings

The board has had meetings four times in 2023. On the agenda for the Board has been to update the webpages, change name, travel stipends, information folder about NBS (paper/digital). Not all tasks are finished and we will continue the work on these in 2024.
Support for travel stipends and conferences
Due to severe economic situation of the society we have not supported any travel stipends or conferences in 2023.

Economy

The society's economy is weak but stable. The board has continued to take measures to reduce expenses. We think the economic situation is under control, but still need to increase income to have the possibility to support local initiatives and travel stipends to a large extent.

E. Approval of the revised accounts of NBS, NBS-nytt and Contact Meeting 2022

Proposed decision from the board:
The general assembly received information about the financial situation and accounts of NBS and NBS-nytt for 2023.
The general assembly approves a continued low cost profile for 2024. Approval of the accounts will await revision of the accounts and will take place in an extraordinary general assembly in the spring of 2024.
An extraordinary general assembly will be held digitally when the revised accounts are ready.

F. Election of president and/or general secretary.

Rein Aasland has been President elect for 1 year now and will now be elected as President of NBS.

The secretary general needs a replacement. We have been unable to identify candiates for the secretary general elect position.

Proposed decision from the board:
Rein Aasland will take over as President of NBS now. We thank Klara Stensvåg for her efforts as President from 2020 to 2024.

Rein Aasland officially took over as president of NBS. He will receive the mighty NBS-gavel at the gala dinner. Each local node of NBS has to propose a member for an election committee that will try to recruit a new secretary general for NBS.

G Matters proposed by the board:

A. Discussion of objectives and laws of NBS
The objectives and laws of NBS has been evolving continuously since the start of the society. The board wants a discussion in light of the recent name change and how we best can move forward. The board will for the next general assembly propose eventual changes to the laws reflecting the discussions in the general assembly.

Rein opened the discussion: The bioscience field is larger than ever, the community seems to be shrinking. How can we make the organization become more relevant?

Suggestions and thoughts from the audience:

- Winter meeting is a key to increasing the society – increase the meeting attendance.
- NBS could open for group memberships. Department memberships? Group membership was useful for the neurological society.
- Research institutes are not represented – Norce, SINTEF, høyskoler etc. Should target these institutions in advertisement. The meeting is very University centric – try to recruit industry – nice for students – institutions will follow.
- A second yearly NBS-event that needs registration. Could also be local: NBS Oslo winter poster session in February – with poster session – pizza and one invited speaker. – Even a company
- Write collaboration testimonials from NBS meetings in NBS nytt. Tell your colleagues!
- Automatic renewal of membership
- Sale of NBS merchandise.
- Have potential to use our international collaborations better, or potentially reconsider membership (IUMBM is very expensive),

H Other matters received:

No matters received

I. Approval of the proposed budget

Budget for 2024 was approved by the general assembly
Orientations

J. NBS-nytt: the editor informs about NBS Nytt 2023.

The magazine needs more financing. More people could contribute with content – local branches must contribute.

K Report from NBS local branches.

- Oslo
- Bergen
- Trondheim
- Tromsø
- Ås

Report from the local branches will be included in the next NBS Nytt.

L NBS Contact meeting 2025: Trondheim

The next meeting will be in Røros 23.-26 Januar 2025

M NBS Contact meeting 2026: Bergen

Nothing planned yet, NBS Bergen will put together a committee this spring and start planning.

Poster prize winner from NBS contact meeting

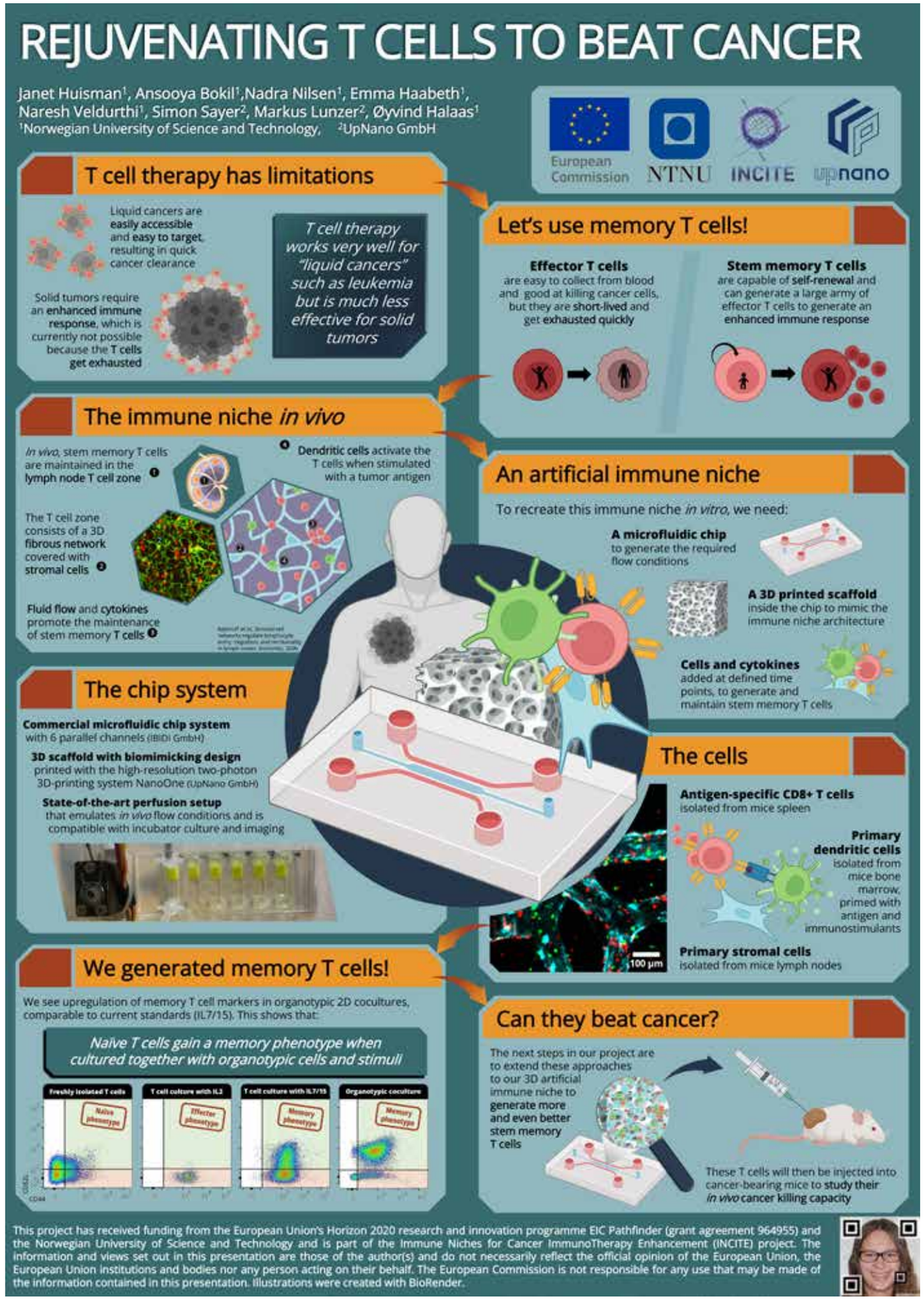
Rejuvenating T cells to beat cancer

JANET HUISMAN
PhD candidate,
Department of Clinical and Molecular Medicine, NTNU

Immunotherapies have great potential to cure cancer, as they use the patient's own immune system to target and destroy cancer cells. However, current methods to generate cancer-specific cytotoxic T cells lack effectiveness when treating solid tumors, mostly because of T cell exhaustion. Rejuvenating T cells towards T memory stem cells (Tscm) is a promising solution for this problem, but as of today no proper and safe method to generate these stem cells exists. Since Tscm in vivo develop within the lymph node, in the presence of stromal cells and dendritic cells (DCs), we propose that recreating this immune niche in vitro will promote T cell rejuvenation. The goal of my PhD project is therefore to create such a living, dynamic, 3D immune niche microenvironment designed to rejuvenate T cells for advanced adoptive T cell therapy, which has never been attempted before.

Together with the INCITE consortium, we have developed scaffolds that mimic the complex 3D architecture found in secondary lymphoid organs. These scaffolds are then 3D printed inside a microfluidic chip using the high-resolution two-photon 3D printing system NanoOne Bio (UpNano GmbH). Physiological flow rates are controlled by a RingPump setup, which is compatible with incubator culture, confocal imaging and allows for seeding and recirculation of the cells in the system. Stromal cells and antigen loaded DCs isolated from mice are sequentially seeded on the scaffolds before addition of naïve T cells. The T cells are kept in the niche for 4-8 days to allow for antigen-specific T cell priming and differentiation. Preliminary analysis of biomarker expression by the T cells collected from the immune niche indicates that this microenvironment can promote differentiation of T cells towards a memory phenotype. With further development, we believe these artificial immune niches can revolutionize the use of adoptive T cell therapy against solid tumors and expand our knowledge of immune cell interactions in the lymph node microenvironment.

Janet Huisman is a PhD candidate at the Department of Clinical and Molecular Medicine at NTNU in Trondheim. Her work is carried out under the supervision of Professor Øyvind Halaas and is adjoined to the EIC Horizon2020 Pathfinder project INCITE (grant agreement 964955). Additional information can be found at https://www.incite.eu.com.



Irisdiagnostikk

Mange anser Biorabiaten for å være bortimot ufeilbar. Kanskje ikke så underlig, når man betrakter den lange listen over briljante innfall, uventede løsninger på store samfunnsproblemer, geniale forskningsresultater og politiske genistreker som hans navn er knyttet til. Men stilt overfor slike påstander, rister han bare stille på hodet. Han vet bedre enn noen at han er langt fra feilfri. Og det største feilen han har begått gjennom hele sin karriere er, sier han, et manglende åpent sinn. Alt for lett har han avfeid alternative filosofiers forsøk på å belyse tilværelsens mange viderverdigheter. For femti år siden lo han bare hånlig av bekjente som bedrev regelmessig faste som et middel for bedre helse. I dag sørger han nitid for å ha 16 timer i døgnet uten mat, i håp om at det virkelig er slik at den økte konsentrasjonen av ketonlegemer i blodet fører til en foryngelse av blodårenes endotelceller. Yogateknikker avfeide han som orientalsk visvas, mens han i dag øver iherdig på å puste riktig og øke toleransen for karbondioksid og gjøre blodårene mykere (pust inn, pust ut, vent i 20 sekunder, pust inn igjen, gjenta, gjenta). Så gang på gang har han blitt nødt til å ta et oppgjør med sine gamle fordommer.

Og nå står en ny fordom for tur: irisdiagnostikken. I følge Store medisinske leksikon ble irisdiagnostikk først presentert av ungareren Ignatz von Peczely i 1881. Han hevdet at alle kroppsdeler og organer er representert i øyets regnbuehinne og at sykdom og ubalanse kan observeres som fargeforandringer, ringer eller mørke felter. Som de fleste naturvitenskapere har Biorabiaten ansett dette for rent svada og nok et eksempel på kyniske behandleres utnyttelse av syke mennesker. Men nå viser altså en fersk artikkel i Science Translational Medicine at det kan være noe fornuft i dette likevel. Artikkelen omhandler riktignok en annen av øyets hinner: retina eller netthinnen. Med utgangspunkt i et stort materiale av optisk koherenstomografibilder fra UK Biobank, som inneholder informasjon om hvordan helsen utviklet seg hos pasientene som bildene ble tatt av, og ved bruk av maskinlæring fant forskerne ut at det var klare korrelasjoner mellom tykkelsen av de ni lagene i retina og fremtidige sykdomstilstander. Og ikke bare øyesykdommer, men også fremtidige sykdommer i hjerte, nyrer, lunger og nervesystem. Når undersøkelser av retina kan avsløre så mye om pasientens helsetilstand, er det rimelig å tro, mener Biorabiaten, at en undersøkelse av regnbuehinnen, som er lettere tilgjengelig uten behov for avansert utstyr, også kan fortelle en erfaren terapeut mye. Så nok en av naturvitenskapens bastioner er i ferd med å falle, sukker han.

Hva blir det neste? Biorabiaten ser for seg at fotsoneterapien kan bli den neste alternative behandlingsformen som kan bli stueren. Ifølge fotsoneterapeutene gjenspeiler forskjellige soner av fotsålen forskjellige deler av kroppen, sykdom vil manifestere seg ved at det oppstår ømme punkter i fotsålen, og sykdommen kan behandles ved bruk av forskjellige fotmassasjeteknikker. Her bør det bygges opp en prospektiv biobank hvor et stort antall individer får kartlagt ømme punkter under føttene og følges over en tiårsperiode for utvikling av eventuelle sykdommer. Ved bruk av kunstig intelligens vil dette kunne avsløre eventuelle diagnostiske fortrinn ved metoden. Når først dette er etablert, må det utføres en omfattende studie for å evaluere den terapeutiske effekten av fotmassasje. Biorabiaten innrømmer at dette vil kreve mye ressurser, men påpeker at et positivt resultat vil føre til kolossale innsparinger for Helsenorge.

Vil flere bastioner falle? Hva med homeopatien? Biorabiaten tror ikke på at storstilte studier av denne behandlingsformen vil være etisk forsvarlig. Derimot kan kvantefysiske fremskritt, for eksempel når det gjelder sammenfiltring av partikler, bidra til å gi denne behandlingsformen et naturvitenskapelig fundament. «Hvis du har en løsning som inneholder ett eneste molekyl av et stoff og du deler løsningen i to. I hvilken halvpart befinner molekylet seg i? Den ene? Den andre? Eller begge?». Med et skjevt smil avslutter Biorabiaten samtalen.

PhDs Oslo
November 2023-Mars 2024

Andreas Hagen Røssevold

Photo: Åsne Rambøl Hillestad, UiO

Cand.med. Andreas Hagen Røssevold at Institute of Clinical Medicine defended the thesis "Immunotherapy and immunological biomarkers in breast cancer" for the degree of PhD on Feb. 9, 2024. The work was carried out under supervision of Senior Consultant Jon Amund Kyte, Oslo University Hospital

Summary

Immune checkpoint inhibitors are drugs that block inhibitory immune signals, which may restore anti-tumor immunity and induce durable tumor responses across numerous cancer types. While cytotoxic chemotherapy agents were primarily developed to target rapidly dividing malignant cells, a large body of literature suggests that the immune system plays an integral part in their clinical efficacy. A proposed link between cytotoxic effects and anti-tumor immune responses is the concept of immunogenic cell death (ICD), a stress-induced regulated cell death that triggers the establishment of an adaptive immune response against the dead and dying cells.

In the current thesis, we present results from two randomized clinical phase 2 trials that combine ICD-inducing chemotherapy with immune checkpoint inhibitors (ICI) in metastatic breast cancer.

The ALICE trial showed that the addition of PD-L1 inhibitor atezolizumab to chemotherapy improved progression-free survival in triple-negative breast cancer, irrespective of tumor PD-L1 expression. The combination was safe and tolerable, and patients in the combination arm reported improved quality of life compared to the control arm. ALICE was the first study to suggest benefit from adding ICI to chemotherapy in PD-L1-negative disease and the results were published in Nature Medicine in 2022.

The ICON trial evaluated the addition of ipilimumab and nivolumab to chemotherapy in hormone receptor-positive breast cancer. The study showed that concomitant chemotherapy and ICI led to increased toxicity without improvement of clinical outcome. ICI administered after chemotherapy gave clinical responses in a proportion of patients.

In the third study of the thesis, we show that the analysis of tumor immune gene expression may identify early-stage basal-like breast cancer patients with high anti-tumor immune activity and an excellent prognosis.

These results may contribute to more effective and individualized treatment of breast cancer in the future.

Erik Egeland Christensen

Photo: Private

Cand.med. Erik Egeland Christensen at Institute of Clinical Medicine defended the thesis "Towards improved sepsis delineation" for the degree of PhD on Jan. 19, 2024. The work was carried out under supervision of Researcher Aleksander Rygh Holten, University of Oslo.

Summary

Sepsis is a highly lethal syndrome of organ failure, infection and dysregulated immune responses. Despite extensive research, the treatment of sepsis has remained largely unchanged for decades. The lack of scientific progress in the field has been attributed to the enormous heterogenicity of sepsis patients: a given therapeutic approach may benefit certain sepsis patients, but harm others. A major challenge is identifying sepsis patients and what differentiates them.

In this thesis, we aim to approach some of the challenges in defining organ failures in sepsis and identifying infection early, and we compare immune cell phenotypes in sepsis caused by SARS-CoV-2 and other pathogens.

There is no gold standard test for sepsis and the diagnosis depends on definitions and clinical criteria that describe the syndrome. Sepsis was re-defined in 2016 as "a life-threatening organ dysfunction caused by a dysregulated host response to infection". This is however not readily identifiable in the clinic, and clinical criteria were established after testing and validation in large cohorts, assessing the ability of organ failure scoring systems to predict death among patients with suspected infections. An acute increase in Sequential organ failure assessment (SOFA) score of 2 or more was chosen to diagnose sepsis. These studies could not, however, separate acute and chronic organ failures, with potential implications for the operationalization of the sepsis diagnosis. In paper I, we found that a significant proportion of the SOFA score was present before the acute illness (chronic organ failures). This implies a significant risk of over-diagnosing chronically ill patients with sepsis. Furthermore, we found that taking only acute organ failure into account when calculating SOFA compromises the score's ability to predict death, which is problematic when mortality prediction was the reason for selecting SOFA in the first place.

Studies of infection biomarkers in patients with possible sepsis in the emergency department have shown highly variable results and no biomarkers are currently recommended for diagnosing infection in this patient group. In paper II, we investigated how well the biomarkers calprotectin, c-reactive protein, interleukin 6 and procalcitonin detected infection in potentially septic patients. Interleukin 6 and c-reactive protein were the two best biomarkers, and could potentially improve and in many cases correct the emergency department physician's decision on whether or not to start antibiotic treatment. Interestingly, interleukin 6 and c-reactive protein were frequently discordant, and may thus complement each other in the detection of infection.

In paper III, we explored phenotypes and gene expression in mononuclear peripheral immune cells in patients with sepsis and various severities of Covid-19. We found that leukocyte phenotypes were associated with Covid-19 severity: T cell IL-7 receptor expression was lower in critically ill Covid-19 patients. In the same patient group, we found lower HLA-DR and higher PD-L1 expression in monocytes and lower frequencies of non-classical monocytes than in less critically ill Covid-19 patients. This suggests a central role of monocytes in the development of critical Covid-19. Furthermore, the patterns of PD-L1 and IL-7 receptor expression may explain mechanisms of lymphopenia in these patients, and may constitute therapeutic targets in Covid-19-associated lymphopenia.

SARS-CoV-2 can, like many bacteria and other viruses, cause sepsis, but whether the causative microbe explains the heterogenicity seen in sepsis patients remains unknown. We therefore compared the characteristics of immune cells in intensive care unit (ICU) patients with sepsis caused by SARS-CoV-2 and bacteria, and found a more homogenous immune cell compartment in the former group. This may help to explain why a number of immunotherapies have been shown to improve survival in patients with severe Covid-19, but not in patients with sepsis caused by other microbes.

Saykat Das

Photo: Øystein Horgmo, UiO

M.Sc. Saykat Das at Institute of Clinical Medicine defended the thesis "Gluten-induced autoantibody response against transglutaminase 2 and transglutaminase 3 in coeliac disease and dermatitis herpetiformis" for the degree of PhD on Feb. 5, 2024. The work was carried out under supervision of Professor Ludvig Magne Sollid, University of Oslo.

Summary

Dermatitis herpetiformis (DH), an inflammatory skin condition, is considered an extraintestinal manifestation of celiac disease (CeD). Individuals carrying HLA-DQ2.5, HLA-DQ8, or HLA-DQ2.2 are predisposed to both CeD and DH. In both conditions, harmful immune responses to dietary gluten are driven by presentation of deamidated peptides by these HLA-DQ allotypes to CD4+ T cells.

CeD is hallmarked by an autoantibody response to transglutaminase 2 (TG2), while DH patients develop autoantibodies to TG2 and also to transglutaminase 3 (TG3). Recent research on autoantibodies against TG2 has been extensive, but little is known about the anti-TG3 autoantibody response in DH. Our studies reveal that anti-TG2 and anti-TG3 autoantibodies are specific with no cross-reactivity. Anti-TG3 autoantibodies exhibit biased usage of IGHV2-5 heavy chains paired with IGKV4-1 light chains, suggesting selection of B cells for plasma cell development. Monoclonal antibodies generated from single TG3-specific gut plasma cells recognize three epitope regions.

TG2 and TG3, both being Ca2+ dependent enzymes, modify peptide glutamine residues through deamidation or transamidation. Unlike TG2, active TG3 requires proteolytic cleavage to become catalytically active. X-ray crystallography analysis shows that catalytically active TG3 undergoes a conformational change detaching the C-terminal C1 and C2 domains and exposing the active site to react with substrate. DH-derived antibodies recognize the enzyme-substrate intermediate conformation of TG3 without the C1C2 domains, supporting a model for TG3-specific B cell activation via help from gluten specific CD4+ T cells facilitated by hapten-carrier like complexes of TG3 and gluten peptides.

We studied the naive TG2 binding B-cell receptor (BCR)-repertoire in CeD patients and healthy donors. Surprisingly, the naive BCR-repertoire does not fully reflect the BCR-repertoire of TG2 binding gut plasma cells in patients with active CeD. Our findings suggest that rare naive B cells binding to a specific TG2 epitope are selectively activated due to their superior interaction with gluten-specific CD4+ T cells through hapten-carrier mechanism.

In summary, our work provides mechanistic insight into autoantibody development against TG3 and TG2. Similar mechanisms may be involved in other autoantibody responses, inspiring future studies on other autoimmune diseases.

PhDs Oslo
November 2023-Mars 2024

Sima Zolfaghari

Photo: Ine Eriksen, UiO

Cand.med. Sima Zolfaghari at Institute of Clinical Medicine defended the thesis "Investigations on regulation, signaling properties, and functions of CCN5" for the degree of PhD on Jan. 18, 2024. The work was carried out under supervision of Professor II Håvard Attramadal, University of Oslo.

Summary

Our research group has previously shown that CCN2 is secreted as a preproprotein that requires proteolytic activation in order to release the biologically active entity. CCN5 is a divergent member of the cellular communication network factor (CCN) family that has been shown to elicit opposite or inverse actions to that of CCN2 and to inhibit myocardial collagen deposition in chronic pressure overload of the heart.

A major aim of this thesis is to elucidate to what extent CCN5 requires proteolytic processing in order to release the biologically active entity. Another aim was to explore the regulation and cellular distribution of the CCN5 protein in wound healing following myocardial infarction.

In this thesis, we demonstrated that contrary to the profibrotic immediate early gene CCN2, CCN5 is induced in the late proliferation and maturation phases of tissue injury repair. Furthermore, CCN5 was identified mainly in endothelial cells, fibroblasts, and macrophages of the differentiating scar tissue following myocardial infarction in mice. We further demonstrated that CCN5 is conversely regulated by β2-adrenergic agonists and TNF-α, i.e., factors that are elevated in ischemic heart failure.

Our novel findings revealed that the TSP1 domain of CCN5 constitutes the bioactive entity that recapitulates the regulatory functions previously assigned to full-length CCN5. In addition, the TSP1 domain of CCN5 is capable of inhibiting key signaling pathways previously reported to be stimulated by CCN2, i.e., the AKT and ERK1/2 phosphokinase pathways.

We also found that the TSP1 domain of CCN5 inhibits key profibrotic actions of TGFβ1 on fibroblasts and reverses TGFβ1-stimulated fibroblast-to-myofibroblast differentiation via affecting the canonical TGFβ1-SMAD2/3 signaling pathway.

In conclusion, the TSP1 domain of CCN5 is the bioactive signaling entity that confers the biologic functions of unprocessed CCN5 suggesting that this entity may potentially be used as a new pharmacologic intervention to halt progressive fibrosis.

Inger Marie Bowitz Lothe

Cand.med. Inger Marie Bowitz Lothe at Institute of Clinical Medicine defended the thesis "Pancreatic and Periampullary Adenocarcinomas: A Clinical, Hisotpathological and Molecular Study" for the degree of PhD on Dec. 14, 2023. The work was carried out under supervision of Group Leader Elin H. Kure, Oslo University Hospital.

Summary

Pancreatic and periampullary adenocarcinomas – the significance of tumor origin and histological subtype for clinical outcome

Pancreatic and periampullary adenocarcinomas arise from four nearby anatomical locations in the pancreatic head all associated with high mortality. The most frequent, with the worst overall survival, is pancreatic adenocarcinoma. The only curative treatment is surgery, and efficient treatment options are lacking.

The aims of the thesis were to analyze the pattern and management of recurrence and survival of ampullary and duodenal adenocarcinomas. Further, to explore the clinical relevance of the histological subtypes pancreatobiliary and intestinal, by identifying potential prognostic molecular biomarkers linked to histological subtypes and site of origin, In addition, facilitate biological and preclinical studies by generating primary patient derived xenograft cell models from pancreatic adenocarcinomas.

The identified prognostic molecular markers emphasize that these tumors are distinct at the level of histopathology and subtype could be included when treating these patients. Patient derived xenografts and corresponding cell lines were successfully established. The cell lines had the capacity to form new cancerous tumors with the same molecular expression pattern as the chemotherapy naïve primary tumors.

Rannveig Viste

Photo: Marit Skram

MSc Rannveig Viste at Institute of Clinical Medicine defended the thesis "Narcolepsy after the H1N1 pandemic – an immunogenetic approach for understanding post-H1N1 narcolepsy type 1 pathogenesis" for the degree of PhD on Dec. 8, 2023. The

Summary

Irisin er et hormon som produseres av muskler og frigjøres til blod under muskelsammentrekning etter f. eks fysisk trening. Irisin er den ekstracellulære delen til det større membranbundne proteinet, *fibronectin type III domain-containing protein 5* (FNDC5). Økte nivåer av irisin kan påvirke kroppsvekten, senke insulinnivået og bidra til å bedre glukosetoleranse. Selv om FNDC5/irisin hovedsakelig uttrykkes i skjelettmuskulatur, har det også blitt oppdaget i forskjellige vev som hjertet, hjernen, leveren, skjoldbruskkjertelen m. m. Imidlertid er uttrykket og de biologiske effektene av FNDC5/irisin i tannvev lite studert.

Periodontiet, de fire vevene som holder tennene på plass; tannkjøtt, sement, alveolar ben og periodontal ligament (PDL), er konstant utsatt for mekaniske stimuli indusert av tygging, tale, gnissing av tenner, etc. Slike mekaniske stimuli kan ligne det skjelettmuskulatur utsettes for. Siden tidligere studier har vist de gunstige effektene av irisin på periodontale ligament celler hadde dette doktorgradsarbeidet som mål å studere uttrykket og reguleringen av FNDC5/irisin i orale vev, og i tillegg identifisere om rekombinant irisin kan påvirke eksperimentell ortodontisk tannbevegelse, og de mulige mekanismene bak det.

Dataene viste at FNDC5/irisin ble uttrykt og regulert forskjellig i ulike periodontale ligamentceller og vev. Injeksjon av rekombinant irisin i en ortodontisk rottemodell reduserte tennenes mulighet for bevegelse. Immunfluorescensfarging viste at den reduserte tannbevegelsen kan skyldes at vevet ble mer likt ben med økt ekstracellulær matrix (ECM) avsetning.

Det ble deretter produsert 3D vevs-lignende strukturer av humane celler i en roterende inkubator, og irisin økte de mekaniske egenskapene (nanoindentation), ECM og cellenes potensiale for å kunne utvikle seg til ben (RT-PCR, Affymetrix, Luminex). Irisin påvirket uttrykket av et stort antall gener og ulike signalveier assosiert med proliferasjon, differensiering, og ekstracellulær matrix metabolisme. Funnene i disse 3D vevsstrukturene understøttet den reduserte ortodontiske tannbevegelsen som ble observert i dyrestudiet, og antyder at irisin kan ha en rolle i ombygging og reparasjon av periodontiet.

Mari Roberts Spildrejorde

Photo: Øystein Horgmo, UiO

M.Sc. Mari Roberts Spildrejorde at Institute of Clinical Medicine defended the thesis "Assessing the safety of medications during pregnancy using multiomics and a neuronal differentiation model of early human neurodevelopment" for the degree of PhD on Dec. 7, 2023. The work was carried out under supervision of Group Leader Robert Lyle, Oslo University Hospital

Summary

Medications taken during pregnancy may reach the developing fetus and interfere with neurodevelopmental processes, and possibly increase the risk of disease in later life. Epigenetic modifications have been proposed as a mechanism linking medication exposure to adverse neurodevelopmental outcomes. This thesis examines the effect of paracetamol and citalopram on epigenetic and gene expression patterns during neuronal differentiation of human embryonic stem cells.

The thesis presents an in vitro neuronal differentiation protocol of human embryonic stem cells optimised for neuropharmacological applications. A molecular timeline of gene expression and epigenetic patterns at four timepoints during neuronal differentiation was developed. Next, the neuronal differentiation model was employed to study the effect of paracetamol exposure at therapeutic concentrations. Paracetamol induced changes in gene expression, DNA methylation and chromatin accessibility in genes important for brain development and function, as well as for genes implicated in neurodevelopmental disorders, indicating possible paracetamol-mediated mechanisms. An overlap was found with changes in DNA methylation in the cord blood of children with ADHD exposed to paracetamol during pregnancy.

Exposure to therapeutic concentrations of citalopram demonstrated time- and dose-dependent effects on gene expression associated with brain functions and depression, but not DNA methylation, suggesting the involvement of alternative gene regulatory mechanisms.

This research provides insights into how medications used by pregnant women can impact fetal brain development. This is crucial knowledge for better understanding the mechanisms, safety, and long-term effects of medication use during pregnancy.

PhDs Oslo
November 2023-Mars 2024

Marte Heimli

Photo: Åsne Rambøl Hillestad, UiO

M.Sc. Marte Heimli at Institute of Clinical Medicine defended the thesis "A multi-modal approach to human thymocyte development and selection for establishment of self-tolerance" for the degree of PhD on Nov. 24, 2023. The work was carried out under supervision of Professor Benedicte Alexandra Lie, University of Oslo.

Summary

During development in the thymus, immature T cells, or thymocytes, undergo selection to ensure that only those without self-reactive potential complete maturation. Self-reactive thymocytes may alternatively diverge into unconventional, agonist selected T cell lineages. Unconventional T cells have immune-modulating functions, and hold potential for cell-based therapies for patients with autoimmune disease. However, their development, regulation, and cellular heterogeneity must be understood for safe and effective implementation.

The aim of this thesis was to enhance current understanding of thymocyte development and selection, emphasising cells undergoing agonist selection and the implicated antigen-presenting and stromal cell populations. Single-cell and spatially resolved technologies were used to characterise cells from young paediatric thymi, permitting elucidation of gene expression profiles, immune receptor repertoires, chromatin landscapes, and spatial organisation.

The findings indicate that divergence into two unconventional T cell lineages, regulatory T cells (Tregs) and CD8αα T cells, occur prior to differentiation of mature, conventional T cells. For Tregs, a second developmental pathway at a later developmental time point was also suggested. Divergence at distinct time points was proposed to be influenced by signalling from distinct populations of antigen-presenting and stromal cells. These populations, in particular thymic epithelial cells, were assessed in detail, revealing previously unrecognised heterogeneity. Further, T cell receptors (TCRs) on the suggested CD8αα precursors exhibited features previously described for TCRs on mature CD8αα T cells, implying that the TCR may also influence developmental decisions.

Overall, the studies increased understanding of factors implicated in development of unconventional T cell populations, which may facilitate future effort towards therapeutic implementations.

Marie Synnøve Haugsten Hansen

Photo: Nicolas Tourrenc

M.Sc. Marie Synnøve Haugsten Hansen at Institute of Clinical Medicine defended the thesis "Calcium dependent arrhythmia mechanisms in CPVT and ischemia-reperfusion" for the degree of PhD on Nov. 15, 2023. The work was carried out under supervision of Professor Mathis Korseberg Stokke, University of Oslo

Summary

Altered Ca2+ handling in cardiomyocytes can lead to arrhythmias in the rare, inherited disorder catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1), and in the early reperfusion phase following a myocardial infarction (MI). In CPVT1 Ca2+ leak from the sarcoplasmic reticulum occurs due to gain-of-function mutations in the cardiac Ryanodine receptor (RyR2), and targeting the upstream regulatory protein Ca2+/calmodulin-dependent protein kinase II (CaMKII), has been suggested as a potential therapeutic target. However, it is not known whether such interventions could lead to a separate arrhythmia mechanism, called Ca2+ alternans instead. In the reperfusion phase following MI, the return of oxygenated blood leads to acidosis, increased oxidative stress and Ca2+ overload in the heart. This may cause Ca2+ leak through RyR2, and be arrhythmogenic. Increased activation of CaMKII by both Ca2+ and oxidation is believed to contribute to this process, but evidence is lacking. Marie Haugsten Hansen aimed to provide further insights into the mechanisms behind Ca2+ dependent arrhythmias in CPVT1 and ischemia-reperfusion (IR), and a basis for future improvement in risk stratification, prevention and treatment strategies. The main findings of this work support CaMKII as an interesting target for future treatment strategies in CPVT and IR. Indeed, CaMKII and ROS were demonstrated as important contributors to arrhythmias in these conditions, however, oxidation of M281/282 on CaMKII was not found to be a critical factor in the development of early reperfusion arrhythmias. Testing of antioxidant therapy resulted in protection from Ca2+ dependent arrhythmias in mice. However, antioxidant therapy in a clinically relevant pig model of MI did not protect against myocardial damage or reperfusion arrhythmias. This demonstrates important species differences and the need for testing initial findings for antiarrhythmic therapy in larger animals.

Espen Basmo Ellingsen

Cand.med. Espen Basmo Ellingsen at Institute of Clinical Medicine defended the thesis "Telomerase-based therapeutic vaccination and checkpoint inhibition: Characterization of the induced immune response and impact on the tumor microenvironment" for the degree of PhD on Nov. 10, 2023. The work was carried out under supervision of Professor Eivind Hovig, University of Oslo.

Summary

This project aimed to elucidate the immunological mechanisms induced by the investigational treatment UV1 in combination with checkpoint inhibition. UV1, a cancer vaccine candidate developed by the Norwegian company Ultimovacs, was the subject of our investigation. The research included a comprehensive analysis of the induced T cell response through cell culturing and phenotyping. By administering UV1, we stimulate an immune response against telomerase, hypothesizing that a CD4+ T cell response against a critical tumor-associated antigen will lead to enhanced cancer cell killing and improved clinical outcomes for treated patients.

We compared the dynamics of the immune response across three of these phase 1 studies involving UV1, either as a stand-alone treatment or in combination with the checkpoint inhibitor ipilimumab. Our findings revealed that the immune responses occurred with higher frequency and at a faster rate when UV1 was administered alongside ipilimumab. In all trials, the immune response exhibited remarkable persistence, lasting for several years and displaying substantial fluctuations. Notably, these fluctuations often correlated with clinical events, such as the initiation of new checkpoint inhibitors. Our research also demonstrated that patients who exhibited immune responses experienced prolonged survival compared to those who did not. In our investigations, we examined the expression of the vaccine's target, telomerase, by analyzing tissue samples from patients' tumors. We also examined the infiltration of immune cells before and after treatment, shedding light on their role in the immune response. Our latest study with UV1 focused on its combination with another immunotherapy, pembrolizumab, involving 30 patients with malignant melanoma. This combined treatment proved to be safe for patients and exhibited promising efficacy, even among those for whom reduced responsiveness to immunotherapy would typically be expected.

Hanna Wan Mun Chan

Photo: Carina Knudsen, UiO

M.Sc. Hanna Wan Mun Chan at Institute of Basic Medical Sciences defended the thesis "TSAd as a target for therapy: TSAd-SH2 domain interactions in T cells" for the degree of PhD on Jan. 26, 2024. The work was carried out under supervision of Professor Anne Spurkland, University of Oslo.

Summary

T cells play a crucial role in the immune system to combat infections and have been exploited for use in immunotherapies. Intracellular signalling networks ensure that T cells respond in an appropriate and sufficient manner. Characterising the mechanisms of how T cell intracellular signalling pathways are regulated is imperative in understanding T cell function.

In this work, we focused on an adaptor protein implicated in T cell intracellular signalling, T cell specific adaptor protein (TSAd), whose functional role remains elusive. TSAd contains several regions for protein interaction, including the Src homology 2 domain (SH2). Given the importance of SH2 domains in phosphotyrosine (pTyr) signalling, the aim of this work was to further characterise TSAd SH2 interactions and its functional role in T cells.

Firstly, we established a work-flow to introduce point mutations in Jurkat T cells by using CRISPR/Cas9 gene editing. Using this work-flow, we attempted to render the TSAd-SH2 domain non-functional by mutating its conserved arginine. Secondly, we characterised the interactome of the TSAd SH2 domain in an unbiased manner. Using affinity-purification mass spectrometry and biochemical methods, we identified two novel ligands of TSAd, namely DOK2 and PTPN11. The sites of interaction were determined and binding was dependent on a functional TSAd SH2 domain. Lastly, the functional role of TSAd in T cells was addressed using TSAd deficient T cells. We confirmed some previously reported phenotypes as well as addressed discrepancies of the data in the field in light of the novel interactome data. Overall, our findings provide further insight into which signalling pathway(s) that TSAd may be implicated in. This insight may aid in future development of immunotherapies as well as elucidating mechanisms of T cell driven pathologies.

PhDs Oslo
November 2023-Mars 2024

Ida Monshaugen

Photo: Kim Groustra Vjus

M.Sc. Ida Monshaugen at Institute of Basic Medical Sciences defended the thesis "The regulatory role of N1-methyladenosine in tRNA in the development of urothelial carcinoma of the bladder" for the degree of PhD on Dec. 8, 2023. The work was carried out under supervision of Senior Research Investigator Rune Ougland, Bærum sykehus, Vestre Viken.

Summary

Urothelial carcinoma of the bladder (BLCA) is a disease of high occurrence globally. A high recurrence frequency often necessitates lifelong control schemes of invasive examinations and harsh treatment, reducing the life quality of patients.

Several RNA-modifying proteins have been associated with BLCA, and a link between transfer RNA (tRNA) modifications and the disease has been proposed. N1-methyladenosine (m1A) is a highly abundant tRNA modification, and it has been suggested that m1A and m1A-regulatory proteins contribute to tumour development and progression, yet the contribution in BLCA pathogenesis remains elusive.

The aims of the thesis were to profile the abundance and m1A modification status of non-micro smallRNAs in BLCA primary tumours to gain a deeper insight into the non-micro smallRNA landscape in BLCA, and to further determine the function of m1A base modification in regulation of mRNA functions.

An updated workflow of small RNA-sequencing using a reverse transcriptase more prone to read through the m1A modification (TGIRT-based sRNA-Seq) was applied in the thesis. TGIRT-based sRNA-Seq of surgical specimens of non-muscle invasive BLCA revealed that non-micro sRNAs are abundantly expressed in BLCA. Particularly in one class of non-micro smallRNAs, tRNA-derived fragments (tRFs), the m1A modification is highly prevalent and dependent on the methyltransferase complex TRMT6/TRMT61A which is up-regulated in BLCA.

The m1A modification level in a subset of tRFs was found to prevent the tRFs from silencing target genes involved in the unfolded protein response pathway in BLCA cells, resulting in increased expression of those genes promoting cell survival. This proposes a mechanism by which the elevation of TRMT6/TRMT61A can impact gene expression through RNA base modification.

Investigations of the biological role of TRMT6/TRMT61A in BLCA cell lines suggested that the m1A methyltransferase complex plays an oncogenic role in BLCA by being involved in desensitising BLCA cells against cellular stress.

The results raises the possibility that inhibiting the TRMT6/TRMT61A enzyme or reversing the aberrant m1A modification in target tRFs may be a new approach to treat BLCA. The findings present tRFs as potential candidates for BLCA targeting strategy requiring further research. Collectively, these findings support that continued efforts in understanding the role of m1A modification status in small RNAs could present opportunities for future therapeutic and diagnostic strategies.

Kine Ødegård Hanssen

Phot: mn.uio.no

Kine Ødegård Hanssen defended the thesis "Effects of perineuronal nets on conductive and capacitive properties of neurons: Computational studies" for the degree of PhD at the University of Oslo, Faculty of Mathematics and Natural Sciences on Dec. 11, 2023. The work was carried out under supervision of Professor Anders Malthe-Sørenssen and Professor Gaute T. Einevoll, Department of Physics, University of Oslo, Norway, Professor Marianne Fyhn and Dr. Geir Halnes, Department of Biosciences, University of Oslo, Norway.

Summary

Perineuronal nets are protein structures that encapsulate certain neurons in the brain. They have been linked to memory retention and proposed to have a barrier function, as well as affecting properties of the neuronal membrane. As technical and monetary restrictions may limit experimental efforts, simulations can help shed light on the nets' function. On a shorter scale, diffusion inside the nets can be studied through coarse-grained molecular dynamics simulations. From this, the resistance of the nets can be derived, providing an estimate as to how good of a barrier the nets actually are. If the nets are good barriers, the distance between ions on the inside and outside of the cell increases, leading to a reduced capacitance. This change may affect how the neuron fires electrical signals. The capacitance enters as a parameter in models of entire neurons, along with conductances through channels in the membrane. In this thesis, Kine Ødegård Hanssen uses these tools to study properties of the nets. She finds that the nets restrict diffusion, but that their resistance is small compared to the membrane resistance. She simulates neurons with and without nets, and finds that a capacitance change alone cannot explain results found in the literature.

Mayes Alswady-Hoff

Photo: Michelle Christin Foss, STAMI

Master of Molecular Biosciences Mayes Alswady-Hoff at Institute of Basic Medical Sciences defended the thesis "Mechanisms of carcinogenic potential of occupational exposure to manufactured nanomaterials" for the degree of PhD on Dec. 7, 2023. The work was carried out under supervision of Lead Research Professor Shan Narui, STAMI – The National Institute of Occupational Health in Norway.

Summary

Advances in nanotechnology have made it possible to manufacture a wide range of nanomaterials with considerable improved properties and applications. The small particles are found in everything from cosmetic products like toothpaste and shampoo to electronics, textiles, paint, and packaging. However, due to the increased manufacturing and use of nanomaterials in industrial production, concerns have been raised about potential adverse health effects among exposed workers. Occupational exposure to nanomaterials may occur during design, manufacturing, utilization, and waste handling, with inhalation as the main exposure route.

The aim of this thesis was to investigate cellular transformation ability and mechanisms of long-term exposure to titanium dioxide (TiO2) and multiwalled carbon nanotubes (MWCNT) using low and occupationally relevant doses. The results showed that both TiO2 and MWCNT had the ability to transform human bronchial epithelial cells, indicating their carcinogenic potential. These nanomaterials also induced changes in lipidomic and proteomic profiles, cell cycle, cell survival, and cell death mechanisms. The thesis contributes to a better understanding of the biological impact at the molecular level following exposure to nanomaterials.

Gaoyang Li

Photo: Qichao Lan University of Oslo.

M.Sc. Gaoyang Li at Institute of Basic Medical Sciences defended the thesis "Rheumatoid arthritis (RA) - Genetic association and prediction of MTX efficacy in human RA patients and deciphering a murine model for testing novel RA drugs" for the degree of PhD on Nov. 24, 2023. The work was carried out under supervision of Professor Bjørn Steen Skålhegg,

Summary

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects 0.5-1% of the world's population, primarily causing joint inflammation and pain. Without sufficient therapy, it can result in significant disability and reduced quality of life. Early diagnosis and effective treatment will reduce symptoms and disease progression. Despite that methotrexate (MTX) have revolutionized RA treatment and is used as a first-line treatment, only half of the RA patients respond positively to this medicine. MTX efficacy has been shown to be associated with polymorphisms in genes encoding proteins involved in MTX metabolism. Li has investigated the relationship between MTX efficacy identified by various clinical outcomes, and specific gene polymorphisms associated with MTX metabolism. Li has also developed a model using machine-learning approaches to predict MTX efficacy with demographic, clinical and genetic polymorphism variables at baseline. The model could predict remission status with the clinical variable RA impact of disease (RAID) as the most robust predictor, while MTX metabolism associated genetic polymorphisms showed a general limited contribution. To explore potential novel therapeutic strategies and to establish a drug screening murine platform, Li examined the involvement of immune cellular components and pharmacological effects in a novel murine arthritic model, the Delayed-Type Hypersensitivity Arthritis model. Li documented the dynamic involvement of proinflammatory T cells and activated B cells in the inflammatory process and the effects of two widely prescribed anti-RA drugs. This animal model for RA holds promise for screening, identifying and optimizing novel drugs targeting RA. Overall, Li's study identified associations between MTX efficacy and genetic variations, proposed a machine-learning prediction model for RA remission status, and deciphered an appropriate murine model for drug screening and RA therapeutic development.

PhDs Oslo
November 2023-Mars 2024

Adrián Lopez-Porras

Photo: Private

Adrián Lopez-Porras at the Department of Biosciences, Faculty of Mathematics and Natural Sciences, defended the thesis "Adaptive Humoral Immunity in Atlantic cod (Gadus morhua), a Teleost Fish with Evolutionary Losses of MHCII and CD4" for the degree of PhD on Feb. 9, 2024. The work was carried out under supervision of Professor Finn-Eirik Johansen, Department of Biosciences, University of Oslo and Professor Shuo-Wang Qiao, Department of Immunology, University of Oslo.

Summary

The Atlantic cod possesses a unique immune system, with an evolutionary loss of key genes crucial for antibody responses to conventional vaccines and combating infectious diseases in other vertebrates. This work found an alternative vaccination strategy rendering the Atlantic cod capable of producing a strong and durable antibody response. Specific antibodies induced by vaccination with dead bacteria were shown to effectively protect Atlantic cod from otherwise lethal bacterial infection. The researchers transferred antibodies from vaccinated cod to unvaccinated ones and showed that this provided protection to unvaccinated fish against bacterial infection. This insight is crucial for vaccine development, revealing that the Atlantic cod can effectively deploy antibodies for defense against bacteria, even in the absence of certain immune system components found in other vertebrates. Additionally, an advancement in this research was the development of a new gene-editing platform, utilizing the CRISPR/Cas9 tool, to selectively deactivate specific genes in the Atlantic cod. This is a pivotal development for future research into the cod's immune system, as it enables researchers to investigate the consequences of removing specific immune cells such as T cells.

The Atlantic cod has lost key genes in the immune system required for antibody response to conventional vaccines in other vertebrates. This PhD research found an alternative vaccination strategy for induction of strong antibody responses and showed that specific antibodies play a vital role in conferring protection against bacterial infections. Additionally, a significant advancement in this study was the adoption of CRISPR/Cas9 gene-editing technology in the Atlantic cod, thereby enabling more in-depth future studies of its immune system.

Sudhagar Balasundaram

Photo: Private

Sudhagar Balasundaram at the Department of Biosciences, Faculty of Mathematics and Natural Sciences, defended the thesis "Ecological transitions and evolutionary genomics of the invasive brown rot fungus Serpula lacrymans" for the degree of PhD on Dec. 15, 2023. The work was carried out under supervision of Professor Håvard Kauserud and Associate Professor Inger Skrede, Department of Biosciences, University of Oslo.

Summary

This thesis explores the ecological transitions and evolutionary genomics of the dry rot fungus Serpula lacrymans and related species within the Serpulaceae family. Phylogenetics, evolutionary genomic approaches, as well as experimental analyses of wood decay and competition abilities, were used to better understand how Serpula lacrymans has transitioned from living in nature to the built environment. First, the number of genetic markers required to identify cryptic species in Serpula was examined, which revealed that a few, phylogenetically informative DNA markers, can provide a solid demarcation of cryptic species. Then, the ecological adaptations that the destructive house-invading fungus Serpula lacrymans var. lacrymans has gone through in order to colonize woody substrates inside the built environment were examined. Comparative genome analyses showed that var. lacrymans displayed very effective wood decay, while its wild relative, Serpula himantioides showed better competitor abilities. The analysis indicated that var. lacrymans is an ecological specialist with poor competitive ability against other fungi. The study also analyzed the evolution of the wood decay machinery in various Serpula lineages in relation to colonizing various substrates, i.e. its niche breadth. The analysis confirmed that var. lacrymans is more specialized for the rapid decay of specific substrates (spruce), while Serpula himantioides seems to be more of a generalist. The specialist var. lacrymans might be less dependent on nitrogen-intensive enzymatic degradation compared to the more generalist relative Serpula himantioides.

Ane Haarr

Photo: private

Ane Haarr at the Department of Biosciences, Faculty of Mathematics and Natural Sciences, defended the thesis "Occurrence and dynamics of organic contaminants in Tanzanian biota: legacies of past production and emerging concerns" for the degree of PhD on Dec. 13, 2023. The work was carried out under supervision of Professor Katrine Borgå, Department of Biosciences, University of Oslo, Professor Jan Ludvig Lyche, Norwegian University of Life Sciences (NMBU) and Professor Anders Ruus, Research Institute for Water and the Environment (NIVA) & Department of Biosciences, University of Oslo

Summary

Research on persistent organic pollutants (POPs) in tropical regions is scarce, with most efforts concentrated in the Global North. This disparity is concerning as new contaminants are being synthesized and old contaminants find new ways of entering the environment. Of particular worry is the transportation of contaminants within modern consumer goods, such as electronics, from industrialized countries to less industrialized ones. These goods often end up in dumpsites where lack of proper disposal and recycling can lead to environmental contamination. This thesis seeks to expand our understanding of the occurrence and behavior of both legacy and emerging contaminants in Tanzania. The study involves the examination of marine fish, chicken eggs and soil around dumpsites and sites differing in degree of human activity.

The main findings of this thesis include bioaccumulation of POPs in marine biota, seasonal variation of POPs, and their association with human activity. We found no definitive evidence linking e-waste to emerging contaminants in the Tanzanian environment. Instead, these contaminants appear to be widespread, even in areas with no production or extensive use. The presence of both legacy and emerging contaminants in Tanzanian biota necessitates continued research and monitoring efforts, building on the insights this study provides.

Qindong Zhang

Photo: mn.uio.no

Qindong Zhang at the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, defended the thesis "Development of Macrophage-Targeting Strategies for Cancer Immunotherapy" for the degree of PhD on Jan. 25, 2024. The work was carried out under supervision of Group leader, Dr. Philos Mouldy Sioud, Department of Cancer Immunology, Oslo University Hospital and Professor Kristian Berg, Section for Pharmaceutics and Social Pharmacy, Department of Pharmacy, University of Oslo.

Summary

Immunotherapy holds immense promise in treating cancer, yet its effectiveness remains limited in treating most solid tumors due to the presence of immunosuppressive tumor microenvironment (TME), notably M2 macrophages. In her doctoral work, Qindong focused on developing targeting strategies against these cells to enhance cancer immunotherapy.

She discovered prohibitin 1 (PHB1) as a cell surface target recognized by the NW peptide that displayed high affinity for both anti-tumoral M1 and pro-tumoral M2 macrophages. Through screening random peptide phage libraries, several low-affinity phage-displayed peptides that selectively bound to M2 macrophages but not M1 macrophages were selected. By coupling these peptides with a photosensitizer termed IR700, specific elimination of M2 macrophages upon near-infrared light exposure while sparing M1 macrophages was achieved. Surprisingly, even the unmodified M13 phage displayed tropism and exhibited cytotoxicity towards M2 macrophages when combined with IR700 and light irradiation. Additionally, combining IR700 with a phage displaying a cancer-specific peptide killed both cancer cells and M2 macrophages. Furthermore, the investigation into STAT3, pivotal in macrophage polarization, explored PHB chemical ligands with STAT3 inhibition effects, aiming to reprogram M2 macrophages into M1 macrophages. Although STAT3 inhibition did not significantly affect macrophage polarization under their experimental conditions, these findings lay the groundwork for further studies.

Overall, this Ph.D. work advances our understanding of PHBs, demonstrates the utility of phage-displayed peptides in photoimmunotherapy, and investigates the use of PHB ligands in macrophage reprogramming, offering new avenues to reshape the TME for improved cancer immunotherapy.

PhDs Oslo
November 2023-Mars 2024

Verena Mertes

Photo: mn.uio.no

Verena Mertes at the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, defended the thesis "Extracellular vesicles from Gram-negative fish pathogens and their potential vaccine application" for the degree of PhD on Jan. 19, 2024. The work was carried out under supervision of Professor Hanne Cecilie Winther-Larsen, Section for Pharmacology and Pharmaceutical Sciences, Department of Pharmacy, University of Oslo, Professor Dirk Linke, Section for Genetics and Evolutionary Biology, Department of Biosciences, University of Oslo, Senior researcher/ Adjunct professor Duncan Colquhoun, Norwegian Veterinary Institute, Post Doctor, PhD Elia Ciani, Norwegian University of Life Sciences and Researcher, PhD Athanasios Saragliadis, Department of Biosciences, University of Oslo.

Summary

The aquaculture industry is an important producer of food sources worldwide. Continuous vaccine development is required in aquaculture as many pathogens, such as Gram-negative bacteria, pose infection risks. Examples are the pathogenic Gram-negative bacteria *Yersinia ruckeri* and *Francisella* spp. They are the causative agents of the diseases yersiniosis and francisellosis in cultured fish. In this thesis, vaccine approaches based on extracellular vesicles (EVs) against yersiniosis and francisellosis were investigated. EVs display the outer membrane characteristics of the bacterium and can elicit protective immunity in a host against pathogenic bacteria. However, the application of EVs as vaccines requires a high production yield. The studies included in this thesis demonstrate increased EV isolation yield. This was achieved by utilization of bacterial bioengineering as a tool, where both gene deletion and recombinant expression enabled EV production with high yields. In addition, the results from a vaccine trial show important pitfalls in EV-based vaccines and will help to improve future EV-vaccine formulations. Taken together, the studies in this thesis lead to a better understanding of EV-vaccine design against Gram-negative fish pathogens and will help to improve fish welfare in aquaculture by better prevention of disease outbreaks.

Birgit Malene Tovik Wollmann

Photo: Tone Berge

Birgit Malene Tovik Wollmann at the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, defended the thesis "Biomarkers of CYP3A4 and CYP2D6 metabolism in vivo" for the degree of PhD on Jan. 12, 2024. The work was carried out under supervision of Professor Espen Molden, Section for Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo, Head of Department, PhD Tore Haslemo, Center for Psychopharmacology, Diakonhjemmet Hospital, Researcher, PhD Robert Løvsletten Smith, Center for Psychopharmacology, Diakonhjemmet Hospital and MD, Senior researcher, PhD Silje Watterdal Syversen, Clinic of Rheumatology and Research, Diakonhjemmet Hospital.

Summary

Enzymene CYP3A4 og CYP2D6 bryter ned svært mange legemidler, for eksempel blodtrykks- og kolesterolsenkende legemidler, antibiotika og antidepressiver. Det er store individuelle forskjeller i hvor aktive disse enzymene er. Dette fører til ulik legemiddeleksponering mellom pasienter og øker risiko for bivirkninger eller behandlingssvikt. For bedre persontilpasset dosering av legemidler er det derfor behov for biomarkører som kan forutsi aktiviteten til disse enzymene i den enkelte pasient.

I dette prosjektet har vi brukt nivåer av den kroppsegne biomarkøren 4β-hydroksykolesterol som mål på enkeltpasienters CYP3A4-aktivitet. Ved å sammenligne biomarkørnivåer målt i blodprøver fra leddgiktpasienter og pasienter uten kjent betennelse ble det funnet at CYP3A4-aktiviteten var redusert hos pasienter med leddgikt, og at aktiviteten forble uendret hos leddgiktpasientene etter oppstart av behandling. Disse pasientene kan dermed trenge lavere doser av legemidler som nedbrytes av CYP3A4-enzymer.

Videre brukte vi den diettbaserte biomarkøren solanidin som mål på enkeltpasienters CYP2D6-aktivitet. Blodnivåer av solanidin og dens nedbrytningsprodukter identifiserte individer med manglende CYP2D6-aktivitet med 100% nøyaktighet. I tillegg var det sterk sammenheng mellom nedbrytningshastigheten av solanidin og legemidlet risperidon.

Blodmålinger av biomarkørene 4β-hydroksykolesterol og solanidin kan bidra til persontilpasset dosering og bedre behandling med legemidler som brytes ned av CYP3A4 og CYP2D6.

Tianxiang Geng

Photo: private

MSc Tianxiang Geng ved Institutt for klinisk odontologi forsvarte sin avhandling for graden ph.d.: "Ameloblastin and its implications in cancer pathogenesis", 6. des. 2023. Arbeidet ble utført under veiledning av Professor Janne E Reseland, Institutt for klinisk odontologi, Universitetet i Oslo.

Summary

I avhandlingen undersøkes rollen til ekstracellulære matrise proteiner (ECM), med spesielt fokus på Ameloblastin (AMBN), sin rolle i progresjonen til ulike kreftformer. Analysene, som underbygges av de 4 artiklene som er lagt ved, antyder at AMBN kan være en prognostisk indikator ved ulike kreftformer.

Ved bioinformatiske analyser av åpne tilgjengelige data fra ulike former for kreft, viser resultatene at nivået av AMBN spiller en rolle for overlevelse hos pasienter med serøst cystadenokarsinom på eggstokkene. Ytterligere undersøkelser av pasientgrupper med testikkelkreft viser at nivået av AMBN spiller en rolle i forhold til progresjon av kreftformen og for risikoen for tilbakefall. AMBN nivåene spiller ikke bare en rolle relatert til utfall av kreftformer i de ulike reproduksjonsorganene, men også relatert til nevrale vevssvulster. Nevroblastom (NBL) og glioblastom (GBM) er kreftformer som rammer samme vev ved ulike alder, og disse ble valgt for å sjekke om alder på pasientene spiller en rolle i forhold til en sammenheng mellom progresjon av kreft og AMBN uttrykket. Dataene viste at høye uttrykk av AMBN hadde en beskyttende effekt i forhold til progresjonen av begge disse kreftformene. Videre ble gener som korrelerte med AMBN nivåene identifisert som mulige uavhengige prognostiske markører.

I det siste arbeidet ble en mulig mekanisme identifisert ved at det ble påvist en korrelasjon mellom AMBN nivåene og DNA-metylerings mønstrene i vev fra spiserørskreft.

Samlet sett bekreftet de ulike arbeidene avhandlingens hypotese og viste at AMBN kan spille en rolle for utviklingen av kreft på tvers av forskjellige krefttyper, utviklingsstadier og molekylære veier, og fremhever at AMBN ikke bare kan være en allsidig markør for prognose, men også et mulig mål for terapeutisk intervensjon.

Flore Kersten

Photo: mn.uio.no

Flore Kersten at the Department of Chemistry, Faculty of Mathematics and Natural Sciences, defended the thesis "A double-edged sword. AB toxins as attack (cholera toxin) and defense (CCTX2) mechanisms" for the degree of PhD on Feb. 2, 2024. The work was carried out under supervision of Professor Ute Krengel and Senior Engineer Gabriele Cordara, Department of Chemistry, University of Oslo.

Summary

A double-edged sword.

AB toxins are proteins often used by pathogens as an attack molecule. However, some organisms use them as a defense molecule, when threatened by a predator. This PhD thesis provides insights on the understanding of the molecular mechanism of two AB toxins, representing the two distinct roles of attack and defense.

Cholera toxin (CT) and its cousin LT from Escherichia coli are very similar proteins, both causing diarrheal diseases with different severity. In this work, we investigated the structural differences between the two toxins. We then provided a hypothesis to the difference in toxicity and disease severity, which may lead to the design of better therapeutics.

The second target is a fungal toxin: Coprinopsis cinerae toxin 2 (CCTX2). CCTX2 is a defense protein used by the fungus against nematodes attacks. This work describes the molecular structure of the protein and explores its potential function. This work on CCTX2 paves the way for the design of safer nematicides.

PhDs Bergen
November-December 2023

Sissel Norland

Foto/ill.: Ivar Rønnestad, UiB

MSc Sissel Norland at the Department of Biological Sciences, University of Bergen (UiB), defended her PhD thesis "Organization, transformation and activation of the melanocortin system in Atlantic salmon" on November 3rd, 2023. The work was carried out at UIB under the main supervision of Professor Jon Vidar Helvik, and co-supervised by Professor Ivar Rønnestad, Dr. Mariann Eilertsen, and Dr. Ana S. Gomes.

Summary

Atlantic salmon *(Salmo salar)* is a key species in Norwegian aquaculture, but more research is needed to improve the economic and environmental aspects of the industry, including development of feeding regimes that can reduce feed waste. Therefore, it is of interest to understand the mechanisms controlling appetite in fish, so that feed can be administered according to what the fish needs.

The aim of this thesis was to investigate appetite control mechanisms in the Atlantic salmon brain, focusing on the melanocortin system. The results showed that the tuberal hypothalamus is a key brain region in melanocortin-regulated appetite control in salmon, similar to that of mammals. Interestingly, the results also demonstrated that experimental conditions mimicking natural light conditions (periods of light and dark) during early development stimulated a better appetite control in Atlantic salmon fry compared to those reared under constant light or darkness.

Overall, the findings suggest that the need to regulate energy and food intake have resulted in evolutionarily conserved mechanisms of appetite control in the vertebrate hypothalamus, including Atlantic salmon. Additionally, this work also contributed to a better understanding of how salmon regulate their appetite during the first feeding period.

Ronja Göhde

Foto/ill.: Melanie Burford, UiB

MSc Ronja Göhde at the University of Bergen (UiB), defended her PhD thesis "Secretory vesicle protein homologues in choanoflagellates" on December 15th, 2023. The work was carried out at UIB under supervision of Pawel Burkhardt (Michael Sars Centre, UiB) and Aurélia E. Lewis (Department of Biological Sciences, UiB).

Summary

In the nervous system, signals are transmitted from one nerve cell to another via small connections called synapses. Synapses can either be of electrical or chemical nature. The focus of my thesis was on chemical synapses. In these, transmitters are stored in synaptic vesicles, which fuse with the presynaptic membrane to release their cargo. The fusion mechanism of synaptic vesicles with the presynaptic membrane depends on certain proteins, some of which are also part of the synaptic vesicle core. Surprisingly, specific protists possess many of these proteins. These protists are choanoflagellates, which are the closest unicellular relatives of animals. Our results, indicating that core proteins of synaptic vesicles are conserved in choanoflagellates, suggest that these proteins may be older than the nervous system itself. One of these proteins, responsible for vesicle fusion, is synaptobrevin, about which only little was previously known in choanoflagellates. My thesis has shown that there are similarities and differences between the synaptobrevin of choanoflagellates and that of the animal nervous system. Using 3D reconstructions, we found that choanoflagellates have numerous vesicles that can be assigned to different types. Similar to nerve cells, these vesicles show a polar distribution in choanoflagellates. Which of these vesicles are secreted and how remains to be explored. Our results form the basis for future studies on the evolution of synaptic vesicle secretion.

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