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TIDSSKRIFT FOR NORSK BIOKJEMISK SELSKAP

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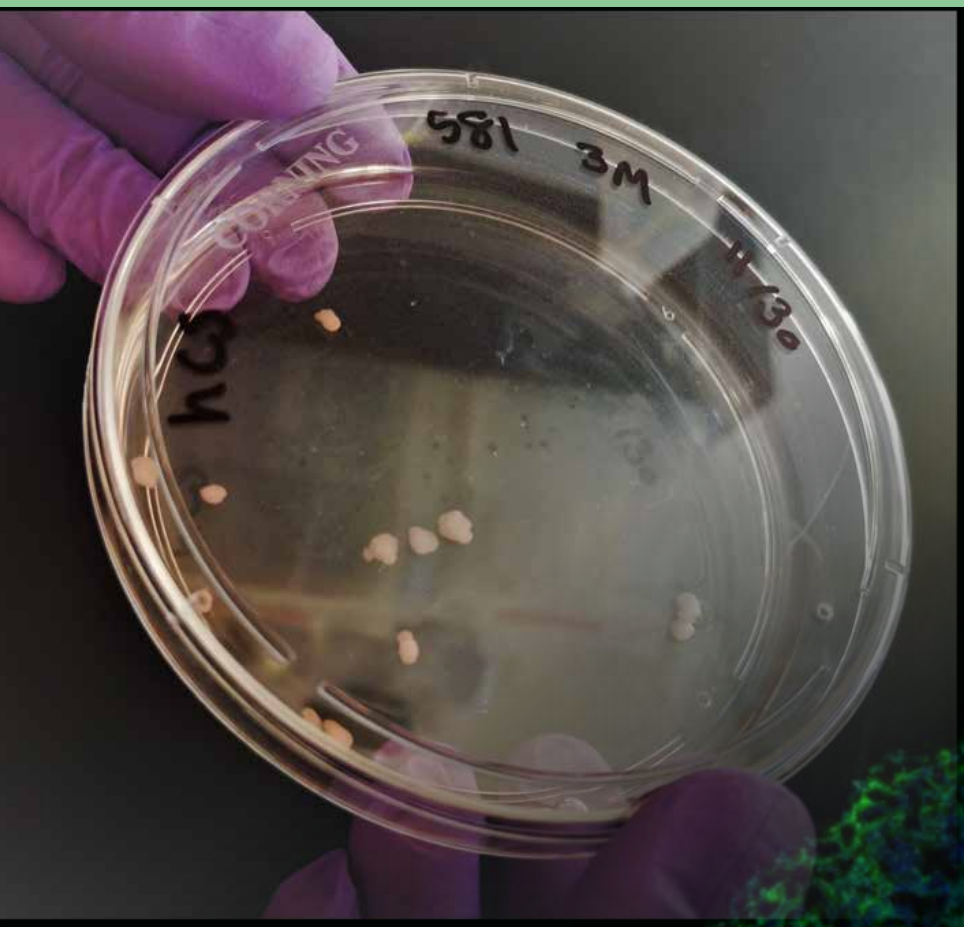

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NBS-Nytt

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LAYOUT

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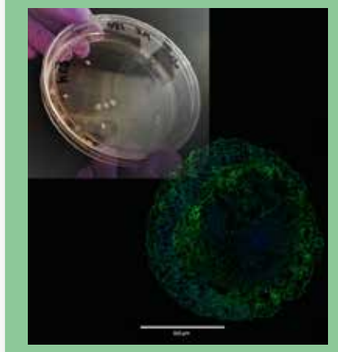
COVER PICTURES

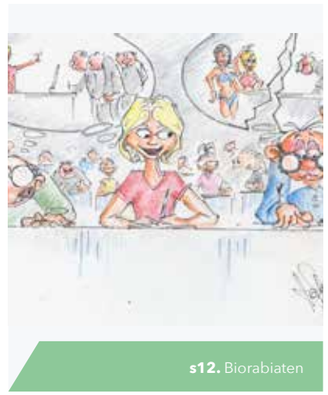


Top Human dorsal forebrain organoids. Bottom: Stained dorsal forebrain for TBR1 (Green), a marker for the dorsal forebrain. Photo: Dr. Balafkan and Dr. Ghorbani

s 6. Norwegian researchers at Yale

INNHOLD

s10. From Chile to Norway



s12. Biorabiaten

Veronica F. Blihovde
Redaktør

Ruth Tamara Montero
Redaktør

Dear readers of NBS-Nytt,
dear friends

In this edition of NBS Nytt, you can read an interview of two Norwegian scientists, who work with precision medicine for psychosis in Bergen, and their experience being visiting researchers at Yale University.

You can then read about how the love of synthetic peptides led a PhD student from Chile all the way to an internship in Norway.

Further, Biorabiaten writes about his experience as an exam invigilator in maths, where he observed a large majority of women taking the exam, and how this led him to a realisation about gene feminism.

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

Are you in the process of writing a paper, starting a new job or got funding for a new project? Write a piece about it for NBS Nytt! It is a great way to increase the reach of your research to relevant scientific communities.

We look forward to meeting you and engaging in interesting discussions about your research projects at the 59th NBS Contact Meeting at Storefjell in January!

Merry Christmas and Happy New Year!

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

The last leader of this president

Klara Stensvåg
President NBS

I will start this leader by reminding you of the coming NBS meeting at Storefjell Resort hotel in January organized by the Oslo branch of NBS. It will be a traditional type of contact meeting. Master and PhD students should particularly be interested since NBS meetings are an excellent arena to make contact and build a network.

What have we achieved as a society the last years?

In January, at the Storefjell meeting, I will cease being the president of the Norwegian Bioscience Society, since we last year choose a president elect, Rein Åsland. Looking back, what have we as a society and the board achieved these last years? In the board, we have worked with several issues that we think have been important to meet challenges, improve and develop NBS.

Some issues have been internally in the board, but others are more visible. The NBS news (NBS nytt) has become digital and should be readable for all. The name of the society is changed, and English has become the official language in our meetings since it is a fact that many of our members do not speak Norwegian fluently. The board has updated the economic system, gone through our association to Federation of European Biochemical Societies (FEBS) and is in the process of changing the web pages. The member fee is still small. Our hope is to make a seamless coordination between these pages and our economic system and to give updated information to all members, old and new. We have local NBS groups that work independently and are responsible for organizing the annual contact meeting every 5th year.

We are a small Society but are convinced that the Society still is essential and should play a role for all bioscience technologists in various parts of Norway, in universities, other research institutions and in biotechnological companies. We hope that we may play a role as life science association, but have we found our perfect role? We aim to discuss how to develop our society and how to increase the outcome for our members. This is ambitious since the field of biosciences is wide and multidisciplinary and there should be interesting topics for all members.

We hope that you will share any idea you may have to increase the impact of NBS!

Significant changes in biotechnology the last years

Not just looking back on NBS, but also to comment on science in the world, what are the biggest recent discoveries, and how have they had any impact on society? As we all know, the world is in constant change, and it is not easy to anticipate the future, i. e. the COVID-19 pandemic. It is always easier to analyse by looking back rather than to make predictions. For instance, the climate change and dramatic increase in temperature, how will that effect development in biotechnology? During the worldwide pandemic, we experienced an accelerated development and manufacturing of vaccines, which is a bioscience achievement.

Yes, we have faced important new discoveries in biotechnological tools in the latest decades. Now it is 11-12 years since the discovery of the CRISPR gene-editing technology. In molecular biotechnology, this technique as a tool has revolutionized the span of what is doable in changing genes or evaluate out effects of changes in gene sequences. The outcomes are visible in curing genetic diseases, increase crop in agriculture and possibilities in synthetic biology.

Another new area, which can be added to the more traditional bioscience areas, is the use of artificial intelligence (AI) and machine learning (ML). They are different, but both technologies are here, and AI is claimed to totally transform the field of biotechnology because of its ability to analyse vast amounts of data, to automate complex processes and suggest intelligent decision makings. One of the areas that is anticipated to change, is medical biotechnology and diagnostics. Drug development with target screening and predictive modelling is mentioned as an important example. In a blog for AI, it is proposed that AI can be employed in analysing genomic data, protein-protein interactions, and medical images, and thus uncover potential therapeutic targets, predict drug effectiveness, diagnose diseases, and make personalized health predictions for uncovering therapeutic targets and predict drug effectiveness in personalized health predictions. Further, analysing big data like in bioinformatics, is claimed to be equally important in computomics in combination with high-throughput omics measurement platforms to deepen our understanding of environmental systems. However, here are challenges, particularly the reproducibility of AI models. In conclusion, the Human-AI interfaces are believed to be crucial for success in biotechnology.

We are facing interesting new years of development within life sciences. Do you agree?

Join the discussions at the NBS meeting and the annual general assembly at Storefjell in January. Hope to see you there!

Best regards, Klara

Norwegian researchers at Yale make strides in precision medicine for psychosis.

Dr. Novin Balafkan and Dr. Sadaf Ghorbani, visiting researchers from Norway, are engaged in a groundbreaking precision medicine project for neuropsychiatric disorders at Yale University. Both are part of the Bergen Psychosis Research Group led by Professor Erik Johnsen at the Mohn Research Center for Regenerative Medicine in Bergen, Norway. Their goal is to utilize human induced pluripotent stem cells (hiPSCs) to model key cellular and molecular features of schizophrenia and to discover new therapeutic targets.

GYRID NYGÅRD
Forskingsavdelinga, Divisjon psykisk helsevern, Haukeland universitetssjukehus

Dr. Novin Balafkan and Dr. Sadaf Ghorbani pictured on the Yale University campus in November, 2023. Photo: Private.

NBS-nytt: *Can you tell us about your project?*

Dr. Balafkan and Dr. Ghorbani: We aim to answer a crucial question: Can genetic variations predict an individual's likelihood of developing specific neuropsychiatric symptoms (like psychosis) and their response to certain medications?

Currently, there are no definitive biomarkers for major psychiatric disorders such as schizophrenia. We treat these diverse conditions with antipsychotics that can have serious side effects and unpredictable effectiveness. Identifying genetic markers predictive of medication response would allow for early diagnosis and more precise, individualized treatment based on each person´s genetic makeup, aligning with precision medicine strategies.

Our research focuses on gene networks related to the effectiveness of antipsychotics, integrating recent discoveries to identify genetic factors influencing response to these medications. We are using hiPSC-technology to create genetically matched neuronal subtypes from two distinct schizophrenia groups experiencing acute psychosis: one responsive to first-line antipsychotics and another that is unresponsive. We`ll conduct various cellular and biochemical assays on these hiPSC-derived neurons to examine their differential responses to antipsychotics in vitro. By comparing the neurons from responders and non-responders post-treatment, we aim to identify core genes linked to antipsychotic response. Our final goal is to explore genetic variants related to these genes and their connection to antipsychotic drug responses.

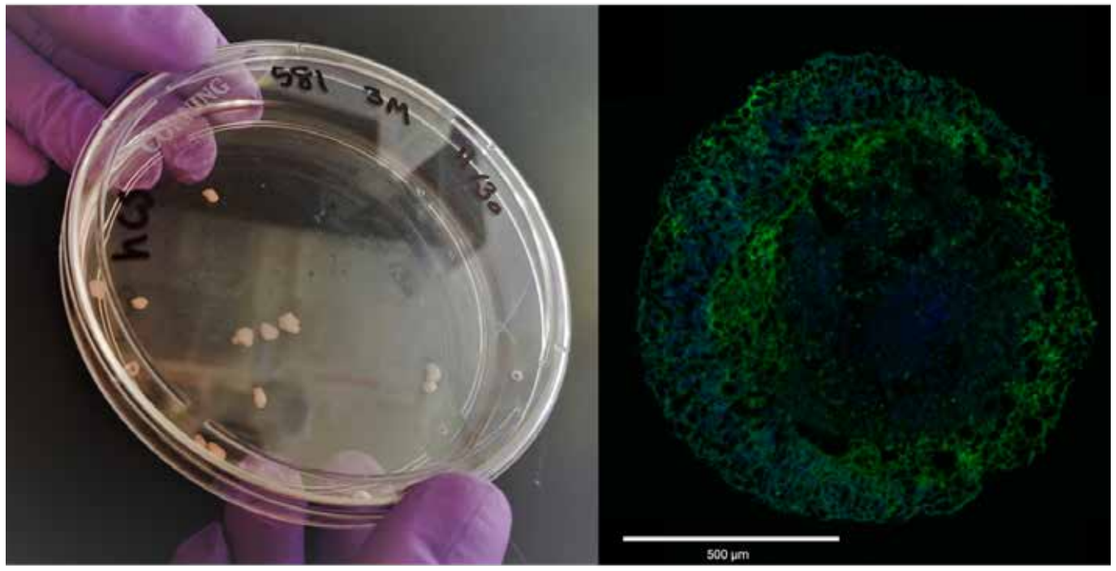
NBS-nytt: *How did you end up at Yale? What are you working on right now and what are your goals?*

Dr. Balafkan: Professor Kristen Brennand is a pioneer in modelling neuropsychiatric disorders using stem cell technologies. Her seminal 2011 publication on modelling aspects of schizophrenia and responses to antipsychotics set a benchmark in the field. When we joined Professor Erik Johansen's project, we recognized the need to develop specific skills to succeed. Consequently, we reached out to Dr. Brennand for her expertise. Graciously, she agreed to collaborate, and we joined her lab at Yale University in 2021.

My current focus is on developing CRISPR screen systems, a gene-editing technique using CRISPR to modulate gene expression. I am particularly interested in studying the loss of function in genes associated with neurodevelopmental disorders, including schizophrenia and autism spectrum disorder (ASD), using pooled CRISPR screens. The primary aim of this research is to investigate how loss of function in these risk genes affects early brain development and to identify common mechanisms across different neurodevelopmental disorders, known as convergence pathways. This project involves extensive collaboration across several prominent research institutes. I am also working with Sadaf on applying this system to her organoids, which are 3D models that recapitulates the cellular composition and structure of the developing human brain.

Dr. Ghorbani: And I am working on determining the protein interaction maps in different neuronal subtypes and explore how mutations associated with schizophrenia and autism will perturb the outline of these maps. This overview will help us identify druggable nodes to reverse the adverse phenotypes associated with perturbed pathways. I am using both 2D cultures of hiPSC-derived neurons as well as brain organoids, which are 3D models of brain cell type composition that mimic the development and structure of the prenatal human brain.

NBS-nytt: *How do you collaborate with*



Left: Human dorsal forebrain organoids. Right: Stained dorsal forebrain for TBR1 (Green), a marker for the dorsal forebrain.
Photo: Dr. Balafkan and Dr. Ghorbani.

each other and with other researchers in the lab?

Dr. Balafkan: Science today is highly interdisciplinary, leading to increased collaboration among labs to tackle complex questions. Our lab at Yale, with over 25 researchers, exemplifies this collaborative spirit. Senior researchers and postdocs often engage in multiple projects: a primary project taking up about 70% of their time, and several collaborative efforts allowing them to contribute as co-authors on colleagues' papers.

Common skills are shared among all lab members, such as generating various types of neurons. However, each team member also possesses unique expertise, whether in assessing neuronal morphology and structure or analysing neuronal function. Since most projects require a combination of skills, we frequently assist one another. Additionally, we conduct weekly and biweekly meetings among all researchers who share common goals, to keep each other updated on our progress. Additionally, we hold weekly lab meetings to share progress and receive feedback from our PI, Dr. Kristen Brennand, an inspiring scientist on the team. We also maintain connections with our Bergen base through biweekly meetings with Dr. Johnsen and the Norwegian team.

Dr. Ghorbani: Yes, we have a very supportive and collaborative environment in the lab while at the same time we are encouraged to develop our own unique niche and skill sets. We are meeting with researchers from the other labs on a weekly basis to discuss our progress on collaborative projects.

NBS-nytt: *You have both received prestigious awards and recognition for your work. Can you tell us about this?*

Dr. Ghorbani: I have received the Seal of Excellence, which is a recognition given to MSCA applicants with proposals scoring 85% or higher. Although my proposal on using peripheral blood mononuclear cells (PBMCs) for drug screening was not funded due to budget constraints, it was acknowledged for its quality and innovation. I also contributed on drafting a successful proposal for the Trond Mohn Foundation, which now covers my salary as a senior researcher at the Mohn Center for Regenerative Medicine.

Dr. Balafkan: I have been awarded the Marie Skłodowska-Curie Action (MSCA) Individual Global Fellowship for 3 years, which is a highly competitive and prestigious fellowship from the European Commission that supports researchers who want to conduct research abroad. This fellowship will enable me to prolong my stay at Yale and continue my collaboration with the Brennand Lab.

NBS-nytt: *You have also been very active in professional development and leadership activities at Yale. Can you share some examples of what you have done?*

Dr. Ghorbani: Sure. I served as the Coordinator for the Professional Development Committee at the Yale Postdoc Association (YPA), which boasts over 1,300 members. During my term, I organized more than 20 workshops and seminars on topics such as grant writing, career planning, networking, communication skills, teaching skills, and mental health. I also ran for the YPA Chair position in 2023, and I was one of only two candidates considered for this role. The student and postdoc-run organizations at Yale are very active which give us a great opportunity to polish our other skill sets besides lab bench techniques.

Dr. Balafkan: I must acknowledge Sadaf's open-mindedness in seeking growth opportunities beyond the lab environment. My focus leans more toward the scientific aspects. For example, our involvement in initiatives like the Scalable and Systematic Neurobiology of Psychiatric and Neurodevelopmental Disorder Risk Genes (SSPsyGene) consortium, thanks to the collaborative nature of our work and our PIs' extensive networks, allows us to engage with leading experts in our field and expand our network beyond Yale. Additionally, our mentorship abilities have grown considerably through guiding various students in the lab over the last two years.

NBS-nytt: *How do you balance your research, professional development, and personal life?*

Dr. Balafkan: It's not easy, but we try to manage our time and prioritize our tasks. Research is not a 9-5 job, especially if you want to work with living creatures as a model. We try to have some fun and relax when we can, but there is no doubt that the definition of work-life balance here is very different from what we experienced in Norway. We try to look at it as a temporary state in our life and as an incredible opportunity to grow in several different aspects.

Dr. Ghorbani: Yes, I can second Novin on that we had to learn a great deal of time management and task prioritization. Specially for us as a husband and wife that work together it is impossible to draw a clear-cut line between personal life and work. When we are feeding cells we talk about dinner and when we are having dinner we talk about our results. I can say we have a balanced scramble which has been working for us. Besides this, we also have a strong support system of labmates, friends and family, who help us cope with the challenges and celebrate the successes.

NBS-nytt: *What are your future plans and aspirations?*

Dr. Ghorbani: We are both planning to return to Norway to continue our research on brain disorders and precision medicine using hiPSCs-derived models. We hope to contribute to the advancement of schizophrenia research and ultimately improve the lives of patients and their families.

Dr. Balafkan: Yes, that's our goal. We are very grateful for the opportunity to work at Yale and learn from the best in the field. We are also excited to bring back our knowledge and skills to Norway, to bridge the field of stem cell research and neuropsychiatric disorders in Bergen and establish our own research groups there. We hope to strengthen our current collaborations and make new ones when the time comes.

NBS-nytt: *Anything else you want to add?*

Dr. Balafkan and Dr. Ghorbani: It's essential to acknowledge that our time at Yale wouldn't have been possible without the substantial support we have received. Dr. Ketil Ødegaard, head of the Mental Health Research Department at Haukeland University Hospital and one of our mentors in Bergen, played a crucial role. We are also deeply thankful to the Trond Mohn Foundation for partly funding our research stay at Yale and to our PI, Professor Erik Johnsen in Norway, for his guidance and tremendous support. Their generosity and commitment to our research goals and aspirations have been invaluable, and our progress would not have been possible without them.

READERS OF NBS-NYTT CAN LEARN MORE BY VISITING THE FOLLOWING WEBPAGES:

1. **Personalized medicine in psychosis treatment:**
   https://www.helse-bergen.no/en/regenerative-medicine
2. **The Mohn Research Center for Regenerative Medicine:**
   https://www.helse-bergen.no/en/regenerative-medicine
3. **The Trond Mohn Foundation:**
   https://mohnfoundation.no/en
4. **Dr. Brennand's lab at Yale and her seminal paper from 2011:**
   https://brennandlab.org
   https://pubmed.ncbi.nlm.nih.gov/21490598

From Chile to Norway: I can not stop falling in love (with science)

My name is Yannick Pombett L., I am a fourth year Ph.D. Chilean student in the joint program Doctorado en Biotecnología between Pontificia Universidad Católica de Valparaíso and Universidad Técnica Federico Santa María (PUCV-UTFSM), and this is my scientific story.

YANNICK POMBETT L.
Norwegian University of Life Sciences (NMBU), Grupo de Marcadores Inmunológicos de Organismos Acuáticos, Instituto de Biología, Pontificia Universidad Católica de Valparaíso (PUCV) and Núcleo Biotecnología Curauma (NBC)

Foto: Ben White/Unsplash.com

I started my scientific career as a Food Engineering student in Pontificia Universidad Católica de Valparaíso, being drawn to the wonders of how the food works in our bodies and how it can affect the health of different organism. My quest to understand how to modulate the different pathways through food ingredients led me to work with synthetic peptides at Núcleo Biotecnología Curauma, where to this day we continue synthesizing peptides on demand as if they were handmade. The most appealing factor (to me) about peptides, is that they have a high selectivity to target molecules, so they can be designed and deployed with virtually any bioactive effect in mind. For example, if you want to block a certain pathway, you can design a peptide to be able to interact with a receptor involved, to attach to a signal molecule, or even to modulate more complex responses (1,2,3). My own first synthesized peptides were designed to have antibacterial activity, but the goal was to improve the base peptide sequence from where they came from to be used in the food industry as a food additive. After this successful and marvelous accomplishment, I decided to step further into the world of science driven by a mix between passion for knowledge and the dream of being able to set my own stone on the scientific scene for others to step-in someday far in the future.

In March 2020, I started my first Ph.D. courses, with a strong focus on continuing my work with bioactive peptides on food. As Chile is a widely known country for the aquaculture of salmonids, there are strong advances from both scientific and production points of view, so as soon as I had an offer to step in, I decided to direct my peptides on the big aquaculture scene. I started working with synthetic antioxidant and iron-chelating peptides, but now related to their effects on the modulations on the macrophage polarization as feed additives, aiming to strengthen the fish to be able to withstand and survive infections, as it is the major cause of mortality in Chilean aquaculture (4). It was during this time where I met my second scientific love (the first being bioactive peptides): cell cultures. I started working with immortalized salmonid cell lines, such as RTS-11, RTgutGC and RTgill-W1. Also, I learned how to extract organs from salmonids and to make primary cultures, which increased even more the spectrum of possibilities to work with. From this point in my scientific life, my path on aquaculture was clearer than ever. In contrary to the human/mammal studies and despite the magnificent work of fish researchers, the fish immune system is still in a nebulous, which implies that there is still a lot of work to do on the subject, so I wanted to put my whole life's work on creating at least one single stone on this topic, to help and lead the greater future works.

After three hardworking years as a Ph.D. student, I was invited for a three months internship to the Norwegian University of Life Sciences (NMBU) by the group Foods of Norway, as they tend to collaborate with my advisor and my thesis project aligned very well with their scope. On my fourth year, we designed and planed my final experiments to be carried out in Norway, and I arrived in August of this year. At the time of writing this article, I am in the last week of my internship, with my final results now in hand, analyzed and ready to be graphed for my scientific publication. Despite being the same techniques, organism models, peptides and instruments, I have learned so much in so little time performing my experiments here at NMBU. Everyone works differently, even when doing the same, everyone has their own focus, so they talk and teach their own interests, and everyone lives differently, which can translate only to enrichment of others. To be able to learn how everyone does the same in a very different way is probably the best conclusion of this internship, as it not something that someone can just read in a journal, it is something that can only be acquired traveling to an other part of the world, and live and work there. I can proudly say that this week I will come back to my country with enough scientific knowledge to share and publish, but also as a person that went through a new phase of discovery and growth, which made me fall even more deeply in love with science, and now Norway of course.

Omsider rettferdighet

Folk flest er ikke klar over at Biorabiaten noen uker hvert år arbeider som eksamensvakt ved privatistekamener. Mange vil være forundret over at en person med såpass høyt aktivitetsnivå og med så mange viktige samfunnsroller tar seg tid til slikt. Han gjør det naturligvis ikke for pengenes skyld, men snarere fordi det gir ham anledning til å gjenopprette dialogen med sitt indre jeg, en dialog som i hverdagen stadig brytes av forstyrrende begivenheter. Tidligere oppnådde han dette ved regelmessige opphold på enerom i tibetanske klostre, men han har kommet til at han som eksamensvakt oppnår det samme og mer til, på en enklere måte.

Eksamensvakter møter på jobb klokken sju om morgenen. Mobiltelefonen skal være avslått, og det er ikke tillatt å nyte medbrakt lesestoff. Når eksamen begynner klokken ni, skal eksamensvaktene holde seg i ro og vokte over de to radene med kandidater som man har blitt tildelt. Regelmessige inspeksjonsrunder langs radene bidrar til en viss variasjon, men stort sett består altså oppgaven i å sitte stille og holde seg våken. Som i tibetanske klostre vil man naturlig gå inn i en meditativ tilstand, men som eksamensvakt er det essensielt at man ikke faller i transe og mister kontakten med omverdenen. Eksamensvakter som går inn i en transetilstand vil raskt bli oppdaget av hovedvaktene og vekkes tilbake til verden på en ytterst ubehagelig måte. Det er denne balansegangen mellom en rik indre dialog og samtidig bevaring av kontakten med den ytre verden som Biorabiaten finner spesielt gunstig for nyopplading av sine kreative evner. Mange av hans mest skjellsettende ideer har kommet til ham under slike omstendigheter. Han ser det også som en enestående anledning til å iaktta mennesker i spesielt krevende situasjoner.

Her om dagen overvåket Biorabiaten en eksamen i matematikk. Av 28 oppmeldte kandidater var det seksten som møtte, og av disse var femten kvinner. Biorabiaten antok først at denne skjevfordelingen skyldtes en statistisk tilfeldighet, men et blikk ut over andre seksjoner som også hadde eksamen i matematikk viste at det var et klart flertall av kvinner blant kandidatene. Da Biorabiaten gikk på skole var det slik at guttene valgte reallinjen og jentene engelsklinjen, så han reflekterte en stund over hva grunnen til en såpass dramatisk endring over såpass få generasjoner kan være. Mange mener at gutter gjennomgående gjør det dårligere på skolen enn jenter fordi undervisningen er tilpasset jentenes evner og behov, men matematikk burde være et fag hvor slike faktorer ikke kan ha særlig stor betydning. Det var da Biorabiaten betraktet kandidatene nærmere at han oppdaget åpenbare forskjeller mellom kjønnene. Kvinnene så ut til å ha full kontroll over eksamenssituasjonen. De satt rolig på stolen, lagde systematiske notater og drakk vann av flasker uten å forstyrre noen. Mennene derimot satt og vred seg på stolene sine med flakkende blikk mens de drakk av bokser med Powerade og Urge på en larmende måte. Da var det som skjellene falt fra Biorabiatens øyne, og han forsto plutselig hvordan alt hang sammen. Selv er han i besittelse av et nærmest plettfritt x-kromosom, men han vet at de fleste av hans medbrødre ikke er like heldige. Hos dem, innså han, fører de ukompenserte gendefektene på x-kromosomet uunngåelig til en manglende evne til å håndtere vanskelige situasjoner og derved til uønsket adferd og til manglende læreevne. Så overskuddet av kvinner som tar matematikkeksamener skyldes ikke at skolesituasjonen er spesielt tilpasset dem, men gjenspeiler rett og slett den reelle forskjellen i læreevne mellom de to kjønn. Biorabiaten innser at dette på mange måter er en skremmende innsikt. Ikke bare er det vanskelig å måtte innrømme at mannen på mange måter er et ufullstendig menneske. Verre er det når man ser på dette i et historisk perspektiv. Tusenvis av generasjoner med umyndiggjøring og utelatelse av de best skikkede har ført til et sivilisasjonsnivå som er ufattelig mye lavere enn det ville vært dersom kvinnene hadde hatt den innflytelsen som deres evner skulle tilsi. Hvor mye bedre tilstand ville verden vært i dersom patriarkatet ikke hele tiden hadde undertrykket dem som burde hatt makten? Hvis søsteren til Niels Henrik Abel hadde fått de samme utdanningsmulighetene som ham, hvor ville matematikken ha befunnet seg i dag? Det er tungt for Biorabiaten å måtte innrømme det, men Germaine Greer og radikalfeministene har rett og har alltid hatt det: verden ville vært bedre uten menn, iallefall uten menn i ledende posisjoner. Folk med genetisk innsikt har innerst inne visst det samme de siste hundre årene, men de fleste har valgt å fortrenge denne innsikten, mens andre (stort sett menn) har forstått det, men valgt å ti stille om det. Men Biorabiaten har kommet til at det nå er på høy tid å ta bladet fra munnen.

Selvsagt må det drastiske tiltak til for å rette opp generasjoner med misskjøtsel av samfunnsutviklingen. Et minstekrav må være tvungen x-kromosomsekvensering av alle samfunnstopper og tvangssperming av alle dem som ikke oppfyller minimumskravene. Og med tanke på kriger og miljøkriser er det viktig at alt dette skjer raskt, i alle fall før neste stortingsvalg. Det er ikke til å unngå at konsekvensene vil bli store, særlig for menn, som brått vil bli revet ut av sine direktør- og disponenttilværelser og må finne seg andre måter å tjene til livets opphold på. Og hva slags jobber vil det være snakk om? Det finnes heldigvis fortsatt samfunnsoppgaver hvor muskler er viktigere enn intelligens, så inntil den påfølgende, raske samfunnsutviklingen gjør slike jobber unødvendige, vil menn fortsatt kunne gjøre nyttig arbeid. Men senere, hva da? Biorabiaten trøster seg med at det finnes eksempler på andre unyttige vesener som likevel får leve gode og fullverdige liv. Katter for eksempel. Så om noen tiår vil menn trolig fungere som en slags kosedyr som sprader rundt og tar seg ut, mens kvinnene tar seg av det nødvendige. Ikke så gæernt det heller!

PhDs Bergen 2023

Victoria Smith Arnesen

Photo: Paul André Sommerfeldt, UiB

Institutt for biomedisin, Medisinsk fakultet, UiB
Hovedveileder:
Professor Martha Chekenya Enger, Institutt for biomedisin
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Tittel på avhandling: Molecular and epigenetic biomarkers of malignant progression in immune subsets and glioblastoma
Avhandlingen ble forsvart 12.05.23

Sammendrag:
Forskningen presentert i dette PhD prosjektet omhandler glioblastom (GBM), en svært ondarted hjernesvulst med få behandlingsalternativ. Forståelse av mekanismene som fører til GBM behandlingsresistens er nødvendig for å utvikle nye terapier. I sitt arbeid har Victoria Arnesen undersøkt tre biomarkører for å gi bedre forståelse av sykdommen.

I den kliniske studien BORTEM-17 blir pasienter med høygradig gliom behandlet med kombinasjonsterapi av bortezomib og temozolomid. Pasienter responderte positivt på behandlingen, en indikasjon for sensibilisering av GBM til temozolomid cellegift, som følge av reduserte mengder MGMT. Pasientene viste styrket immunforsvar i blodet. Flere hadde naturlige drepeceller (NK celler) som uttrykte den aktiverende reseptoren KIR2DS4, som vi tidligere har vist er en god prognostisk biomarkør. Over halvparten av GBM svulster overtrykker NG2/CSPG4, en biomarkør som indikerer dårlig prognose ved å gi cellene resistens mot strålebehandling. Arnesen oppdaget og karakteriserte en genfeil i NG2/CSPG4 som gjorde at proteinet ikke fungerte. Ved bruk av en metode som nøye redigerte arvestoffet i kreftcellene, kunne Arnesen vise at genfeilen førte til hemmet vekst av kreftceller, og ga betydelig forlenget overlevelse.

Forskningen fordyper vår forståelse av hjernesvulstbiologi. Funnene kan lede til utvikling av ny persontilpasset behandling, hvor målrettet terapi vil kunne kombineres med cellegift og stråleterapi for å oppnå langvarig effekt av behandling.

Sofie Søderstrøm

Sofie Søderstrøm at the Institute of Marine Research (IMR) and Department of Biological Sciences, University of Bergen (UiB), defended her PhD thesis *"Effects of the emerging marine aquafeed mycotoxins beauvericin (BEA) and enniatin B (ENNB) in Atlantic Salmon (Salmo salar) – Implications on cellular pathways and functions, and tissue responses"* on the 14th of June 2023. The work was carried out under the main supervision of Dr. Liv Søfteland (IMR), and co-supervised by Dr. Kai Kristoffer Lie (IMR) and Prof. Anne-Katrine Lundebye (IMR/UiB).

Summary:
Enniatin B (ENNB) and Beauvericin (BEA) are toxins produced by molds that target cereal crops. Plant-based feed ingredients can introduce mycotoxins into feed for farmed salmon, raising concerns about fish health and feed safety since these mycotoxins remain unregulated in animal feed due to insufficient knowledge of their toxicity.

In this doctoral research, cell studies with primary liver and kidney cells, along with a feeding study, were conducted to assess the effects of ENNB and BEA on farmed salmon health. Key findings highlight the high toxicity of ENNB and BEA on liver cells, their disruption of iron homeostasis leading to cell death, and their potential to trigger an acute inflammatory response in salmon when present in elevated concentrations. The study also revealed that BEA can interfere with heme biosynthesis in salmon smolts, potentially causing reduced hematocrit and anemic conditions. In contrast, ENNB appeared to induce an acute inflammatory response in the salmon's intestine.

Søderstrøm's research suggests that while exposure to BEA in salmon feed can have harmful effects, the risk is limited due to its low levels and infrequent occurrence. Conversely, exposure to ENNB, which is relatively common in salmon feed, could pose a potential health risk depending on its concentration.

Overall, this work elucidates the underlying mechanisms of toxicity and possible health challenges in salmon linked to these mycotoxins. The work will also contribute to the establishment of future limit values for these mycotoxins in salmon feed, thereby ensuring feed safety and the health of the farmed salmon.

Paula Miramón-Puértolas

Supervisors:
Dr. Patrick Steinmetz, Prof.
Rune Male, Prof. Eric Thompson
Institute: Michael Sars Centre, UiB

Summary:
After birth, new cells are needed for animal bodies to grow and replace damaged cells. New cells originate from adult stem cells, which divide throughout the lifetime of the organism. In humans, adult stem cells are scarce and can only generate one or a few cell types: neural stem cells make new neurons and epithelial stem cells make new skin. In contrast, highly regenerative animals present adult stem cells that divide into diverse cell types, which allows for whole body regeneration. These powerful adult stem cells use proteins such as Vasa and Piwi to retain their broad potential. While sea anemones and corals are known to be highly regenerative and very long lived, their adult stem cells have remained elusive. In this work, we have identified adult stem cells for the very first time in a sea anemone. We traced the presence of Vasa and Piwi proteins in juvenile and adult specimens of the sea anemone *Nematostella vectensis* and found high levels in cells hidden in folds inside the gastric cavity. These cells generate eggs and sperm for the animals to reproduce, but, in addition, our work suggests that these cells also divide into abundant neurons and other cell types. As in other regenerative animals like flatworms, these powerful stem cells may play a key role during regeneration in sea anemones. Our findings set a steppingstone in understanding the stem cell biology of sea anemones and their coral relatives, which may rely on similar cells to regenerate and avoid aging.

PhDs Oslo
September-December 2023

Alice Shwe

Alice Shwe at Faculty of Health Sciences, Oslo Metropolitan University, defended the thesis "Characterization of differentially expressed miRNAs and their predicted target transcripts associated with smoltification and seawater adaptation in Atlantic salmon" for the degree of PhD on Nov. 10, 2023. The work was carried out under supervision of Professor Rune Andreasen, Oslo Metropolitan University and Senior Scientist Tone-Kari Knutsdatter, Norwegian Food Research Institute (Nofima).

Summary

Smoltification, or parr-smolt transformation, is a complex pre-adaptive process of behavioral, developmental, biochemical, and physiological changes that transforms an Atlantic salmon parr living in freshwater (FW) into a seawater (SW)-ready smolt. Successful smoltification is crucial for long-term adaptation to SW, survival, and growth in the sea. In contrast, suboptimal smoltification contributes to higher mortality in the SW phase and increases the risk of poor development, growth, and health. Suboptimal smoltification remains a challenge for Atlantic salmon production in Norway, leading to substantial economic losses. MicroRNAs (miRNAs) are important post-transcriptional regulators of gene expression that play critical roles in various biological processes.

The aim of this project was to investigate whether any Atlantic salmon miRNAs are involved in the regulation of smoltification and seawater adaptation (SWA), and to reveal biological processes that are likely controlled by these particular miRNAs.

High-throughput sequencing of small RNAs in three key organs (head kidney, liver, and gill) of Atlantic salmon was used to characterize changes in miRNA expression associated with smoltification and SW adaptation. This revealed 62, 54, and 18 miRNAs that were differentially expressed (DE) in liver, head kidney, and gill, respectively. Further investigations indicated that these likely are biologically important guide miRNAs (gDE-miRNAs).

Microarray analyses of same materials revealed 5708, 2709, and 2382 mRNAs as differentially expressed in liver, head kidney and gill, respectively. Among these, 2804, 1827, and 747 DE-mRNAs were predicted to be miRNA targets of the gDE-miRNAs in liver, head kidney, and gills, respectively. Gene enrichment analysis of negatively correlated miRNA-mRNA interactions in head kidney showed that they were enriched in important biological processes such as hormone synthesis, stress response, immune response, and ion transport. Furthermore, gene enrichment of DE-miRNA targets in the liver and gills also revealed several enriched biological processes that likely involve post-transcriptional control by the gDE-miRNAs. These include carbohydrate and lipid biosynthesis, amino acid and steroid metabolism, protein transport, response to external stimuli, the immune system, and extracellular organization. Critical genes important in smoltification, such as Cytochrome P4501A (cyp1a1), Na+, K+-ATPase subunits (nkaα1a, nkaα1b and nkaβ), ion transporter cftr1 and aquaporin subunit (aqp11), were among the predicted targets in gill.

Collectively, these results indicate that the characterized gDE-miRNAs are essential post-transcriptional regulators that help FW-adapted parr successfully develop into SW-adapted smolts. The identification of gDE-miRNAs opens up for exploring these miRNAs as biomarkers. The altered expression of such gDE-miRNAs may potentially predict the smoltification status more precisely than the currently used biomarkers. The predicted miRNA targets revealed here need to be verified experimentally, and the gDE-miRNAs and their target genes need to be further studied to reveal the molecular details of this post-transcriptional regulation.

Emilie Steinbakk Ulriksen

Photo: Irene Teixidor Toneu

Cand.med. Emilie Steinbakk Ulriksen at Institute of Clinical Medicine, University of Oslo, defended the thesis "Identification of novel pharmaceutical compounds from traditional Norwegian medicinal plants with focus on immunomodulation and the gut microbiome" for the degree of PhD, Nov 3, 2023. The work was carried out under supervision of Professor Marit Inngjerdingen, University of Oslo.

Summary

Medicinal plants may be sources for novel medicinal compounds. There is a continuous need for new immunomodulatory medications to treat cancer or autoimmune diseases, and we therefore set out to investigate whether we could identify new such compounds from Scandinavian medicinal plants.

Historical records from the early 20th century were used to identify usage of medicinal plants in Scandinavia against indications such as inflammation, upper airway infections and gastrointestinal symptoms. 79 plants were identified, and 23 of these were selected for further studies based on few previous studies. Chemical extraction and fractionation were done to give a crude extract, and two polyphenol and polysaccharide enriched fractions. These samples were tested using immunological assays to assess their effect on immune cell functions. Human fecal cultures were used to test effects on the human microbiota, and mice intestinal organoids were used to test the effect of the bacteria metabolites and plant extracts on gut epithelial cells.

We generally observed an immune stimulatory effect with the polysaccharide enriched fraction compared to the polyphenol enriched fraction. An exception was polyphenols from D. mezereum that were the most potent immune stimulatory substances. We found novel anti-inflammatory compounds by replicating the traditional preparation of Gentiana purpurea roots, and observed a specific immune activating effect in the pectic heteropolysaccharides found in A. archangelica subsp. Archangelica. For the polyphenol fraction of D. mezereum, we also observed a strong positive effect on the gut microbiota and a protective effect on the gut epithelial layer, indicating a potential use as a novel prebiotic.

Lilli Theres Eilertsen Bay

Photo: Gro Elise Rødland

M.Sc. Lilli Theres Eilertsen Bay at Institute of Clinical Medicine, University of Oslo, defended the thesis "Interplay between the transcription machinery and the responses to DNA damage and replication stress" for the degree of PhD, Oct 24, 2023. The work was carried out under supervision of Scientist Helga Bjarnason Landsverk, Oslo University Hospital.

Summary

Human cells are continuously threatened by DNA damage from endogenous sources such as replication stress. To face this threat and prevent cancer, intracellular signaling pathways that promote DNA repair, collectively known as the DNA damage response, have evolved. On the other hand, radiotherapy and several types of chemotherapy kill cancer cells by inducing DNA damage. DNA repair can counteract cell death after such treatments. The DNA damage response is thus very important for cancer progression and treatment.

The transcription machinery is emerging as a new and central factor in the DNA damage response. In this thesis, Bay and colleagues aimed to understand the interplay between the transcription machinery and the responses to DNA damage and replication stress.

Transcription and DNA replication may collide as they share the same template, but how the transcription machinery is regulated to prevent such collisions has remained unclear. By studying the chromatin stability of RNA polymerase II (RNAPII), the main mediator of transcription, Bay and colleagues found a new mechanism to prevent such collisions.

To address how RNAPII is affected by DNA damage, Bay and colleagues developed a new flow cytometry technique. Using it, they gained novel insight into the regulation of the transcription cycle with and without DNA damage.

RNAPII may directly play a role in the DNA damage response by promoting DNA repair. To address this, Bay and colleagues manipulated the phosphorylation levels of RNAPII. They found that phosphorylation of RNAPII promotes binding of several DNA repair factors and likely enhances DNA repair via non-homologous end-joining.

Altogether, the work of this thesis provides new knowledge regarding the interplay between the transcription machinery and the responses to DNA damage and replication stress. Such knowledge provides important insights that may be exploited in cancer treatment in the future.

PhDs Oslo
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Adrian Eek-Mariampillai

Photo: private

M.Sc. Adrian Eek-Mariampillai at Institute of Clinical Medicine, University of Oslo, defended the thesis "Assessment of immunogenic signalling from cancer cells after irradiation and ATR inhibition" for the degree of PhD, Oct. 17, 2023. The work has been carried out under supervision of Scientist and Group Leader Randi G. Syljuåsen, Oslo University Hospital.

Summary

Radiotherapy induces lethal DNA damage to cells, and is widely applied in cancer treatment. Nevertheless, cancers tend to develop radioresistance. Radioresistance may be counteracted by combining the irradiation with inhibitors of DNA repair. Additionally, the resistance may be overcome by increasing tumour immunogenicity.

Irradiation induces both immunosuppressive and -stimulatory effects in the tumour microenvironment. In his doctoral work in cancer radiobiology, Adrian Eek Mariampillai investigated whether the strategy of combining irradiation with DNA repair inhibitors increases the immunogenicity of human cancer cells. In particular, an inhibitor of ATR – a kinase regulating the G2/M cell cycle checkpoint – was employed, with the hypothesis that the co-treatment induces immunogenic cell death (ICD) and an interferon (IFN) response through cGAS-mediated detection of micronuclear DNA. It was also investigated how the co-treatment modulates presentation of the immune checkpoint ligand PD-L1.

By various molecular biology techniques, it was found that the co-treatment increased radiation-induced secretion of IFN-β and the ICD hallmarks ATP secretion and HMGB1 release. A third tested ICD hallmark, surface-presentation of calreticulin, was not increased. Interestingly, addition of a pan-caspase inhibitor increased the IFN secretion and to various extent also ATP secretion, whereas HMGB1 release was dependent on caspase activity.

It was also found that two histone deacetylase inhibitors (HDACi) evaluated in a previous DNA repair inhibitor screen increased radiation-induced presentation of PD-L1. The ATR inhibitor reduced the radiation-induced upregulation of PD-L1, but it did not alleviate the effect of the HDACi, meaning that two different mechanisms are involved. Finally, upregulation of PD-L1 was found to be cell cycle phase dependent.

Nicolas Fragoso Bargas

Photo: Åsne Rambøl Hillestad

M.Sc. Nicolas Fragoso Bargas at Institute of Clinical Medicine, University of Oslo, defended the thesis "DNA Methylation and cardiometabolic health: associations with insulin resistance, folate, and physical activity in pregnancy" for the degree of PhD, Sep. 29, 2023. The work was carried out under supervision of Project Leader Christine Sommer, Oslo University Hospital.

Summary

DNA methylation is a plastic mark that can be affected by genetics and several exposures from an individual's lifestyle and the environment. In this thesis I have explored the association between DNA methylation in maternal peripheral blood leukocytes with insulin resistance, serum folate and physical activity, in a cohort of pregnant women of European and South Asian ethnicity.

In the EPIPREG (Epigenetics in pregnancy) sample (n=480), DNA methylation was quantified in peripheral blood leukocytes in gestational week 28. We identified that methylation at six CpG sites were associated with insulin resistance, whereof five were replicated in external cohorts. Three of the replicated CpG sites were located in the TXNIP gene, which has been previously related with type 2 diabetes and metabolic syndrome. Serum folate have been associated with lower risk for some cardiometabolic outcomes and is vital for DNA methylation maintenance. Thus, DNA methylation has been proposed to be an intermediate mechanism between folate and its associated cardiometabolic phenotypes. Serum folate was associated with methylation at three CpG sites previously not reported in the literature. However, we did not find strong evidence that the CpG sites associated with serum folate were associated with cardiometabolic related traits as well. Lastly, we identified that methylation at several CpG sites were associated with hours of moderate physical activity and two with hours of sedentary behavior. Some of the CpG sites identified across the studies had mQTLs (Methyl quantitative trait loci), indicating that the methylation of these sites could be genetically regulated.

The findings of this thesis could be useful to improve our understanding of the molecular etiology of gestational diabetes, type 2 diabetes and related cardiovascular diseases. Epigenetic signatures may in the future serve as biomarkers for diabetes prevention and point to potential molecular targets for pharmacological interventions.

Yohan Lefol

Ole Christian Klamas

M.Sc. Yohan Lefol at Institute of Clinical Medicine, University of Oslo, defended the thesis "The use of temporality within transcriptomic data" for the degree of PhD, Sep. 28, 2023. The work was carried out under supervision of Researcher Diana Domanska, University of Oslo.

Summary

Transcriptomics is defined as the study of RNA which in turn can give us insight on the expression of genes, that is the degree of activity exerted by each gene. This activity can in turn translate to the understanding of biological elements such as immune or metabolic activity.

One common challenge in medicine is the proper understanding of disease mechanisms, in other words, the 'how' of diseases. Incorrect or incomplete understanding can cause difficulties in both diagnosing, treating, and preventing a disease. Part of the difficulties in understanding diseases is that they are not static, indeed much like how a patient experiences a disease, the disease's mechanism changes from beginning to end. It is therefore important to account for the aspect of time when researching disease mechanisms.

The work presented in this thesis details the steps, and diseases studied, in the development of a bioinformatic pipeline capable of analyzing and aiding in the interpretation of transcriptomic data collected over any number of time points, effectively creating a time line using transcriptomic data.

Lisa Svartdal Normann

Photo: private

MSc Lisa Svartdal Normann at Institute of Clinical Medicine, University of Oslo, defended the thesis "HER2-Positive Breast Cancer and Drug Response in Pre-Clinical Models" for the degree of PhD, Sep. 28, 2023. The work was carried out under supervision of Professor II Kristine Kleivi Sahlberg, Vestre Viken Hospital Trust and University of Oslo

Summary

HER2-positive breast cancer is an aggressive disease that historically was associated with poor outcome. Over the past decades, the prospects for patients with HER2-positive breast cancer have improved due to therapy that directly targets cells overexpressing the tyrosine kinase receptor HER2 (human epidermal growth factor receptor 2). However, some patients do not respond to treatment and need new alternatives. In this thesis, Lisa Svartdal Normann and colleagues have studied new drug combinations pre-clinically to address this.

The main aim of the study has been to identify therapeutic compounds that can sensitize cancer cells to the targeted drugs trastuzumab and lapatinib. Two high-throughput screens were performed using HER2-positive breast cancer cells that respond poorly to targeted therapy. One screen included >270 drugs, and the other screen contained >1600 microRNAs. The endpoint of the screens was to measure viability and protein expression.

The drug screen identified the Src-inhibitor dasatinib as a candidate to reduce cell viability in combination with lapatinib. However, the promising results in vitro were not recapitulated in vivo. Protein expression data from PDX models suggested increased levels of insulin receptor and phosphorylated HER2, which may contribute to the lack of effect in the combination treatment vs control.

The microRNA screen identified miR-101-5p as an agent with promising potential alone and with lapatinib in preventing cell viability in vitro, making it an interesting candidate for further work. Protein expression data from treated cells suggested an effect on signaling pathways such as PI3K-Akt, and initiation of apoptosis. Further, a higher expression level of miR-101-5p in patients was associated with improved breast cancer specific and overall survival.

In short, Normann and colleagues have identified several microRNAs and drugs that inhibited cancer cell viability alone and in combination with lapatinib and/or trastuzumab.

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Alice Ruixue Ai

Photo: private

Master of Dental Medicine Alice Ruixue Ai at Institute of Clinical Medicine, University of Oslo, defended the thesis "Novel mechanisms of NAD+-dependent inhibition of Alzheimer's disease and AI-based technologies in related mechanistic studies and drug discovery" for the degree of Dr. Philos., Sep. 25, 2023. The work was carried out under supervision of Associate Professor Evandro Fei Fang, University of Oslo.

Summary

Dementia is a common disease in older people, affecting 50 million individuals worldwide. The most common form, Alzheimer's disease (AD), has no cure due to limited understanding of its causes. In AD, damage to mitochondria (the cell's powerhouses) and disrupted RNA splicing contribute to disease progression. Nicotinamide adenine dinucleotide (NAD+) is important for brain health. Supplementing NAD+ has shown promise in animal models by preserving mitochondrial function and improving memory. However, its effects on mitochondrial quality control pathways and RNA splicing in AD are still unclear. Artificial intelligence (AI) is used in medicine for analyzing data, diagnosing diseases, and discovering drugs. I combined AI with traditional wet laboratory methods to unveil novel mechanisms on how NAD+ inhibits AD.

I found that increasing NAD+ levels improved mitochondrial health and reduced AD-related issues by helping a protein called ATF5 to move to the cell's nucleus. I also explored NAD+'s influence on RNA splicing. I show NAD+ can normalize abnormal RNA splicing. This normalization may alleviate AD-related problems. Additionally, we developed an AI approach to identify compounds that promote mitophagy (a process that removes damaged mitochondria). Our algorithm identified two promising compounds that induce mitophagy, reduce AD-related problems, and preserve memory in AD models.

NAD+-related clinical trials targeting Alzheimer's disease (AD) are currently underway. These ongoing trials emphasize the significance of conducting more comprehensive mechanistic studies to deepen our understanding of this therapeutic approach. Artificial intelligence (AI) has emerged as a valuable tool in expediting the drug development process, and its integration with wet lab experiments has yielded promising results in the field of medicine. The combination of traditional laboratory research and AI-driven analysis, as I developed in this thesis work, offers a compelling example of how multidisciplinary approaches can contribute to advancements in medical research.

In conclusion, my thesis work provides insights into new causes of AD including compromised NAD+-mitophagy pathway and aberrant RNA splicing capacity. My work provides pre-clinical evidence of restoration of mitochondrial homeostasis and RNA splicing as possible therapeutic strategies against AD.

Kjersti Oppen

Photo: Åsne Rambøll Hillestad

MD Kjersti Oppen at Institute of Clinical Medicine, University of Oslo, defended the thesis "Iron-Related Biomarkers as Predictors of Etiology and Prognosis in Pneumonia" for the degree of PhD, Sep. 15, 2023. The work was carried out under supervision of Professor and Senior Consultant Lars Heggelund, University of Bergen and Vestre Viken HF.

Summary

Iron is indispensable to virtually all living organisms. Consequently, microbes try to exploit human iron to support their expansion, whereas humans aim to restrict the access of iron to invading microbes to prevent infections, a process called "the battle for iron".

During infections, levels of iron and iron-related proteins in the circulation are known to change profoundly. We used biobank material from a prospective cohort of 267 hospitalized community-acquired pneumonia patients to assess the dynamics of iron and iron-related biomarkers during pneumonia, and to explore the potential of such biomarkers to predict microbial etiology and prognosis.

First, high admission levels of hepcidin (iron regulatory hormone) and ferritin (iron storage protein) were more likely in atypical bacterial infections and low values were more likely in viral infections. High ferritin levels were also more likely in atypical than typical bacterial infections.

Second, lower hepcidin levels at admission were associated with increased 5-year mortality compared to higher values, independent of age, sex, and number of comorbid conditions. There was no association with short-term outcome assessed by a combination of ICU admissions and 30-day mortality.

Third, the performance of two analytical principles of hepcidin measurements was compared. The methods were an LC-MS/MS method measuring the bioactive hepcidin-25 and an immunoassay also recognizing smaller isoforms of hepcidin. Different levels were expected from existing knowledge, but in the samples from the acute phase of the pneumonia, the difference increased with increasing hepcidin values.

According to these findings, iron-related biomarkers may aid assessment of microbial etiology (hepcidin and ferritin) and long-term prognosis (hepcidin). To interpret hepcidin measurements correctly, the characteristics of each analytical method and its expected values must be known, also during infections.

Miriam Aarsund Larsen

Photo: Amalie Huth Hovland, UiO

M.Sc. Miriam Aarsund Larsen at Institute of Clinical Medicine, University of Oslo, defended the thesis "Natural killer cell-derived extracellular vesicles and their anti-tumor capacities" for the degree of PhD, Sep. 14, 2023. The work was carried out under supervision of Professor Marit Inngjerdingen, University of Oslo.

Summary

During the past decades immunotherapy has revolutionized the field of cancer treatment. Several cell-based therapies are currently in the clinic as a second-line treatment, and NK-cell based therapies are showing promise in several clinical trials. However, cellular therapies for solid tumors are facing challenges such as poor tumor infiltration and suppressive signals from the tumor microenvironment, hampering the efficacy of the treatment.

We hypothesized that extracellular vesicles (EVs) derived from NK cells could share similar anti-tumor effects, and could act as an alternative therapy form that would be less sensitive to the hostile tumor microenvironment.

The aims of the thesis were to characterize different subpopulations of NK-EVs, their anti-tumor capacities towards solid cancers and how they interact with the cancer cells.

Comparison of cytokine activated primary NK cells or NK cell lines showed that the cellular source was more important for cytotoxicity than the activation protocol used to generate EVs. Also, NK-EVs showed variable sensitivity towards different solid tumor spheroids, indicating a level of specificity towards certain surface structures.

By comparing the microRNA profile across different NK-EV subpopulations we found an enrichment of microRNAs associated with apoptotic pathways in the cytotoxic subpopulation. This indicate that miRNA might be involved in the killing mechanisms of NK-EVs.

Overall, our studies highlight the potential of NK-EVs as future immunotherapy with high anti-tumor capacities and specificity.

PhDs Oslo
September-December 2023

Hamid Khoshfekr Rudsari

Photo: private

M.Sc. Hamid Khoshfekr Rudsari at Institute of Clinical Medicine, University of Oslo, defended the thesis "Modeling Aspects of the Extracellular Vesicle-mediated Bio-nano Communication for Medical Applications" for the degree of PhD, Sep. 12, 2023. The work was carried out under supervision of Professor Ilangko Balasingham, Oslo University Hospital and Norwegian University of Science and Technology.

Summary

Novel drug delivery systems have been proposed utilizing nano-sized extracellular vesicles that are naturally released by all cell types and carry bio-molecules such as genetic acids. These vesicles play a crucial role in intercellular signaling for short- and long-distances in the body, making them relevant to both physiology and pathology. By engineering these vesicles to target specific cells, new possibilities for minimally- and non-invasive drug delivery systems are opened.

A computational methodology to theoretically quantify and analyze bio-nano communication between cells at the cellular level is essential for the development of a drug delivery system. In this thesis, the heart is used as a case study to investigate the basics of bio-nano communication between cells using extracellular vesicles and external control of cells. This research models the release of extracellular vesicles from cardiac cells such as ventricular and atrial cardiomyocytes mediated by intracellular calcium signaling. Also, this research models the propagation of the released extracellular vesicles in the cardiac extracellular matrix and their uptake and internalization at target cells. The use of computer simulations and mathematical modeling is an important aspect of this research as it enables the detailed analysis and predictions of extracellular vesicles' interactions with cells, which is fundamental for the development of efficient drug delivery systems. The research aims to provide tools for:

- Modeling intercellular bio-nano communication and inter-organ signaling,
- Modulation and control of cardiac cells to release extracellular vesicles,
- Prediction of extracellular vesicles propagation in an extracellular matrix,
- Uptake and internalization of extracellular vesicles to target cells,
- Development of novel externally controllable drug delivery systems for cardiac disorders,
- Providing initial results for optimizing experimental studies on extracellular vesicles and potentially other types of nanoparticles.

This research has the following benefits for medical applications:

- The models given in this research are applicable to other types of nano-sized particles/vesicles.
- The models given in this thesis are applicable to estimate the propagation of nano-sized particles such as extracellular vesicles in other types of extracellular matrix in multiple organs in the body.
- The computer models given in this thesis can be developed for a specific type of disease such as chronic heart failure by importing features from imaging methods in preclinical studies.
- The computer models given in this research make the basis of a comprehensive computer model of the human myocardium that can differentiate between different regions of the myocardium such as infarcted and healthy regions of the heart for modeling the treatment of cardiac disorders such as chronic heart failure.
- The models given in this thesis can be developed and expanded for different types of disorders by importing unique features of interest.

Elisabeth Elje

Photo: private

M.Sc. Elisabeth Elje at Institute of Basic Medical Sciences, University of Oslo, defended the thesis "Advanced lung and liver models for hazard characterization of nanomaterials" for the degree of PhD, Oct. 6, 2023. The work was carried out under supervision of Senior Scientist Elise Rundén-Pran, NILU.

Summary

Humans are constantly exposed to particles from the surrounding environment, including nanomaterials (NMs) which are small particles with size <100 nm. After inhalation, some NMs can deposit in the lungs, cross the lung-blood barrier, and reach other target organs such as the liver. New approach methodologies are being developed for hazard assessment of NMs, including advanced in vitro models based on cell cultures in more physiologically relevant conditions. Of special importance is the application of these models for genotoxicity testing, to evaluate the ability of the NMs to alter the genetic information.

The aim of this work was to contribute to the development of advanced lung and liver models, representing a first-contact and secondary target organ of inhaled NMs, respectively. The performance of the models in genotoxicity testing was compared to traditional models.

Advanced lung models were constructed with bronchial or alveolar epithelial cells in mono- or cocultures with endothelial cells and macrophages at the air-liquid interface. An advanced liver model was constructed with hepatocytes cultured in spheroids, allowing increased cell-to-cell interactions and signaling. Both advanced models and traditional models were exposed to NMs or chemicals for 24 hours, before cellular viability, genotoxicity, inter-laboratory variability, and other endpoints were analyzed.

This work has shown that the culturing conditions of the cells affected the toxic response to chemicals and NMs. This thesis contributed to new knowledge on advanced in vitro models by application of genotoxicity testing after NM exposures. Comet assay was applied to HepG2 spheroids and micronucleus assay to ALI cocultures for the first time to our knowledge. The advanced models are promising 3D models for use in genotoxicity studies and can support the hazard and risk assessment of NMs in compliance with the 3R´s for next generation risk assessment.

Alexander Brana Rosic

Photo: Maria Eilertsen

Cand. Med. Alexander Brana Rosic at Institute of Basic Medical Sciences, University of Oslo, defended the thesis "Astrocytic Volume Regulation and Glutamate Dynamics during Cortical Spreading Depression" for the degree of PhD, Sep. 8, 2023. The work was carried out under supervision of Rune Enger, University of Oslo.

Summary

Migraine aura is a collection of perceptual symptoms affecting many migraineurs caused by a phenomenon called cortical spreading depression (CSD). Similar processes can occur in ischemic stroke, subarachnoid hemorrhage and traumatic brain injury called spreading depolarizations.

CSD is a self-propagating, slowly moving wave of depolarization of cells which transiently disarranges the tightly regulated homeostasis in the central nervous system. These disturbances include massive extracellular increase in potassium, overflow of neurotransmitters (e.g., glutamate), cellular swelling and hemodynamic fluctuations. Astrocytes belong to a group of cells in the central nervous system called glial cells and maintain homeostasis of nearly all extracellular compounds, including potassium and glutamate. They also possess specialized processes called astrocytic endfeet which envelop the entire cerebral vasculature.

Albeit glutamate is involved in CSD elicitation and propagation the pathophysiology is not fully understood. Moreover, while CSD-related astrocytic swelling has been reported it remained highly controversial. CSD also caused transitory collapse of perivascular brain waste clearance which potentially could be due to astrocytic endfoot swelling.

This thesis studied the role of astrocytes in regulating glutamate and astrocytes' own cellular volume during CSD using genetically encoded fluorescent sensors and two-photon microscopy in awake and anesthetized transgenic mice.

We demonstrated that CSD induced astrocytic swelling, including in the astrocytic endfeet. The endfoot swelling magnitude was unaffected by the deletion of the water channel aquaporin-4 (AQP4) and was too short to block brain waste clearance. Astrocyte swelling activates the volume-regulated anion channel sub-unit Swell1 and releases glutamate effecting CSD elicitation and propagation. Moreover, we found that the potassium channel Kir4.1 is pivotal for glutamate uptake and alters the threshold to elicit CSD.

PhDs Oslo
September-December 2023

Sverre Grødem

Photo: private

Sverre Grødem at the Department of Biosciences, Faculty of Mathematics and Natural Sciences, University of Oslo, defendes the thesis "Brain Plasticity, Extracellular Matrix Molecules, and Advancements in Calcium Imaging of Neural Activity" for the degree of PhD, Sep. 29, 2023. The work was carried out under supervision of Professor Marianne Fyhn, Department of Biosciences, University of Oslo, Professor Anders Malthe-Sørenssen, Department of Physics, University of Oslo and Professor Kristian Prydz, Department of Biosciences, University of Oslo

Summary

The brain possesses an astounding ability to acquire new memories and retain these memories throughout our lifespan. Consequently, neuronal networks in the brain must exhibit flexibility, or plasticity, adapting and strengthening neuronal connections in response to new learning. Simultaneously, the brain must maintain sufficient stability to solidify the neural connections that underpin long-term memory. The lattice-like structures known as Perineuronal Nets (PNNs), which mainly surround a subset of inhibitory interneurons in the cerebral cortex, are believed to dampen brain plasticity, thus facilitating long-term information retention. In this thesis, I perturb the PNNs by genetically knocking out the PNN component aggrecan solely in these interneurons. Through electrophysiological and behavioral assays and computational modeling, I investigate the potential effects of this perturbation. My findings indicate that while removing aggrecan in developing subjects eliminates PNNs without affecting interneuron function, its removal in adults significantly alters plasticity, suggesting that compensatory mechanisms may mitigate the effect of losing aggrecan and thus PNNs in the germline. These insights shed light on the intricate mechanisms behind memory formation and maintenance in the brain and could contribute to understanding or developing treatments for diseases of the brain, such as Alzheimer's disease. Finally, I develop soma-targeted, genetically-encoded calcium indicator constructs that allow for precise measurement of neuronal activity at the single-cell level in live animals.

Bilal Ünal

Photo: Private

Bilal Ünal at the Department of Biosciences, Faculty of Mathematics and Natural Sciences, University of Oslo, defended the thesis "Molecular characterization of the unfolded protein response and implications for prostate cancer" for the degree of PhD, Sep. 26, 2023. The work was carried out under supervision of Professor Fahri Saatcioglu, Researcher Yang Jin and Professor Cinzia Anita Maria Progida, Department of Biosciences, University of Oslo.

Summary

Cancer is characterized by the ability of cells to adapt and survive under various stress conditions within the tumor microenvironment (TME). One crucial cellular response to these stresses in normal cells which is 'hijacked' in cancer cells is the Unfolded Protein Response (UPR), which plays a vital role in maintaining cellular homeostasis. However, consequences of UPR activation in cancer cells and how this may affect the TME has largely been unexplored.

In this thesis, I characterized the roles of two key proteins in the UPR pathway, IRE1α and PERK, for prostate cancer (PCa) tumor growth and TME remodeling. Through a variety of experimental approaches, I discovered molecular mechanisms underlying immune suppression and tumor growth in the PCa TME, suggesting potential therapeutic strategies to enhance immunotherapy approaches in PCa. I also developed unique cell lines to simultaneously track the activities of UPR pathways in the same cell, which revealed potential novel regulators of the UPR molecular network. Using these novel reporter lines and an in vivo genome-scale CRISPR screen, I uncovered new targets with potential therapeutic impact in PCa, possibly also in other cancers. In summary, this thesis provides novel mechanistic information on the functioning of the UPR with translational implications.

Christiane Færestrand Ellefsen

Photo: mn.uio.no

Christiane Færestrand Ellefsen at the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, defended the thesis "Structural and immunomodulatory properties of β-glucans from edible mushrooms" for the degree of PhD, Nov. 10, 2023. The work was carried out under supervision of Associate professor Anne Berit C. Samuelsen, Section for Pharmaceutical Chemistry, Department of Pharmacy, University of Oslo and Professor Marianne Hiorth, Section for Pharmaceutics and Social Pharmacy, Department of Pharmacy, University of Oslo.

Summary

The cell walls of mushrooms and other fungi consist of β-glucans: long chains of glucose attached via β-glycosidic linkages. Possible interactions with the immune system give fungal β-glucans pharmaceutical potential. This activity depends on the structures of the β-glucans, and whether they are in a soluble or particulate state.

Mushrooms like the king oyster mushroom *(Pleurotus eryngii)* can be grown on agricultural wastes, making them sustainable sources of fungal cell wall material. This thesis investigated the structures and immunomodulatory properties of cell wall β-glucans from the king oyster mushroom. Both water-soluble and water-insoluble β-glucans were identified and characterized. Their structures were found to be typical of fungal β-glucans. A method for dispersing the water-insoluble material was developed using β-glucan material from another edible mushroom: the sheep polypore mushroom *(Albatrellus ovinus)*. All the studied β-glucans interacted with the immune receptor dectin-1a, but they displayed limited activity in immune cell experiments. The results indicate that the mushroom β-glucans may be used to target immune cells. In addition, the developed dispersing method makes the study of poorly water-soluble β-glucans easier. This may lead to increased applicability of such material, for instance in pharmaceutical applications.

Gezime Seferi

Photo: mn.uio.no

Gezime Seferi at the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, defended the thesis "Hippocampal lipid droplets and the gut microbiome: Effects of type 2 diabetes and exercise" for the degree of PhD, Oct. 6, 2023. The work was carried out under supervision of Professor Cecilie Morland, Section for Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo and MD PhD Kaja Nordengen, Department of Neurology, Oslo University Hospital.

Summary

Type 2 Diabetes Mellitus (T2DM) is on the rise due to our modern lifestyle. This condition disturbs our body's ability to handle insulin and affects not only the peripheral parts of our body but also our brain. In our brains it can cause memory issues and depression, while also upsetting the balance of gut microbes that in turn can influence our brain health. Exercise has for a long time been recommended by experts to manage T2DM.

Lipid droplets (LDs) have become increasingly popular in the field of neuroscience. Increase of these spheres filled with lipids in our brain is associated with increased neuroinflammation and neurodegeneration.

This PhD project explored how T2DM impacts the brain and whether exercise can help. It was discovered that certain brain areas are filled with more LD, there are also differences in amount of LD between different types of cells in the brain.

The project also peeked into the bacteria living in our guts. T2DM changes this bacterial community, and exercise has an impact too. Some brain-friendly bacteria decrease in diabetes, but exercise helps restore their population.

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Achal Dhariwal

Photo: private

MSc Achal Dhariwal at the Institute of Oral Biology, University of Oslo, defended the thesis "Exploring the landscape of antimicrobial resistance in microbiomes: a computational metagenomics profiling approach." For the degree of PhD, Oct. 2, 2023. The work was carried out under supervision of Professor Fernanda Petersen, the Institute of Oral Biology, University of Oslo.

Summary (in Norwegian)

Antimikrobiell resistens (AMR) er en økende global bekymring, og utgjør en betydelig trussel mot folkehelsen. Denne resistensen oppstår ofte når bakterier møter antibiotika og utvikler forsvarsmekanismer mot medikamentene. Menneskekroppen sin funksjon avhenger av at tusenvis av bakteriearter trives og samarbeider med oss samtidig. Disse mikrobene danner det menneskelige mikrobiomet. Alle antibiotikaresistensgener (ARG) i dette mikrobiomet utgjør resistomet. Når antibiotika brukes til å behandle infeksjoner, påvirker de ikke bare de sykdomsfremkallende bakteriene, men hele mikrobiomet, og kan endre bakteriesamfunnene og resistomet. Disse utilsiktede konsekvensene av antibiotikabruk har fått økt oppmerksomhet de siste årene. Å undersøke dynamikken til ARG-er i mikrobielle samfunn kan gi innsikt i AMR-fremvekst og spredning. Metagenomics er et banebrytende studiefelt som gir oss mulighet til å dykke dypt inn i hele det mikrobielle samfunn ved å sekvensere deres DNA. Denne oppgaven utnytter metagenomikk for å avdekke utbredelsen og mangfoldet av ARG-er, samt for å undersøke de økologiske bivirkningene av antibiotikabehandlinger for å undersøke utvikling og seleksjon av ARG-er i mikrobielle samfunn.

I første del av prosjektet ble kliniske prøver fra avføringen fra voksne nordmenn undersøkt før, under og etter antibiotika (amoxicillin) eksponering med lang behandlingstid (3 måneder). Funnene viste at langvarig behandling med amoxicillin påvirker mangfoldet og sammensetningen av tarmbakterier signifikant, med reduksjon i mengden av nyttige bakterier umiddelbart etter behandlingen. Disse endringene var imidlertid kortvarige, og ingen signifikante forskjeller ble observert ni måneder etter behandling. I motsetning til dette hadde amoxicillinbehandlingen en varig innvirkning på det menneskelige tarmresistomet. Vi observerte nemlig økt ARG-er mengde og mangfold, som vedvarte minst ni måneder etter behandling.

Potensielt sykdomsfremkallende mikrober som vanligvis er tilstede i humane luftveier er blant de hyppigste årsakene til AMR-relaterte dødsfall. I den andre delen av prosjektet undersøkte vi utviklingen av det humane luftveisresistom og de økologiske konsekvensene av tidlig antibiotikabehandling (ampicillin og gentamicin) hos premature babyer ved bruk av dyp hel-metagenomisk sekvensering. Funnene i denne avhandlingen avslørte utbredt prevalens av ARG i luftveiene hos premature spedbarn fra fødselen. Eksponering for tidlige antibiotikaintervensjoner hos premature babyer førte til forbigående, men betydelig økning av ARG mengde og diversitet i luftveisresistom etter initiert behandling. Dette er en av de første studiene som hittil har gitt omfattende informasjon om egenskapene og dynamikken til resistomutvikling i luftveiene til premature barn. Samlet sett gir funnene fra begge studiene i oppgaven evidensbaserte data om de negative økologiske bivirkningene av antibiotika. De fremhever også behovet for forsterket overvåking av antibiotikabehandlinger og reduksjon av unødvendig antibiotikabruk.

Den tredje delen av denne Ph.d.-oppgaven søker å utvikle et avansert, fritt tilgjengelig, brukervennlig bioinformatikkverktøy kalt ResistoXplorer. Dette verktøyet gjør det mulig for forskere og helsepersonell å analysere, visualisere og tolke metagenomiske resistomdata uten å kreve forkunnskaper om bioinformatikk. Slike verktøy letter anvendelsen av metagenomikkbaserte resistomstudier, og forbedrer vår forståelse av AMR i ulike mikrobielle samfunn, inkludert mennesker, dyr og miljø. ResistoXplorer tilgjengeliggjøre resistomdataanalyse for flere, og fremmer derved hypotesegenerering og kunnskapsgenerering på feltet.

Ved å bygge bro mellom feltene AMR og metagenomikk, har denne forskningen som mål å gi verdifull innsikt og nyttige verktøy for å møte en av de mest presserende globale helsetruslene i vår tid. Kunnskapen som genereres her, spesielt om virkningen av antibiotikaeksponering på menneskelige mikrobielle samfunn, kan føre til innovative strategier for å minimere bivirkninger og bidra til den globale innsatsen for å bekjempe antibiotikaresistens.

Maria Balta

Photo: private

DDS Maria Balta at the Institute of Oral Biology, University of Oslo, defended the thesis "Effects of RvD1 n-3 DPA on oral epithelial cells" for the degree of PhD, Oct. 25, 2023. The work was carried out under supervision of Professor emeritus Karl Schenck, of Oral Biology, University of Oslo and Professor emerita Inger Johanne Schytte Blix, Institute of Clinical Dentistry, University of Oslo.

Summary (in Norwegian)

For å opprettholde god helse, er det essensielt for kroppen å kunne stoppe betennelse, og at dette skjer uten å hemme immunforsvaret. Spesialiserte lipider er involvert i denne prosessen, og de kalles SMP. Disse spesialiserte lipididene kommer fra essensielle flerumettede n-6 eller n-3 fettsyreforløpere. Fettsyreforløpere er molekyler som kroppen kan bruke til å lage nye fettsyrer.

Epitelslimhinnen dekker overflaten i munnhulen, og er en viktig komponent i munnhulens immunforsvar. I tillegg til å være en passiv fysisk barriere, deltar orale epitelceller også aktivt i kommunikasjon mellom immunsystemet og det ytre miljøet ved å generere og utskille bioaktive stoffer som cytokiner, kjemokiner og andre faktorer som er viktig for immunforsvaret.

Målet med denne første studien var å undersøke hvilken effekt et nylig oppdaget SMP hadde på orale epitelceller. Dette SMPet heter resolvin D1n-3 DPA (RvD1n-3 DPA).

I epitelet fant vi reseptorer som bandt seg til det nyoppdagede SMPet. Dette gjaldt reseptorene FPR2/ALX og DRV1/GPR32. I tillegg oppdaget vi, at når vi tilsatte det nyoppdagede SMPet til en gruppe av celler, så oppstod det indre forandringer i cellene som førte til at uttrykket av gener som koder for antimikrobielle peptider ble oppregulert. Dette kan indikere at det nyoppdagede SMPet (RvD1n-3 DPA) kan ha en antibakteriell eller antiviral effekt samt ha et potensiale til å styrke kroppens immunforsvar.

Det er nå bred forståelse av at kroppens manglende evne til å kontrollere og avslutte betennelse er årsak til mange kroniske sykdommer. Derfor var hensikten med den andre studien å bedre forstå hvordan RvD1n-3 DPA kan påvirke funksjonen til epitelceller i munnen når det er en betennelse til stede.

Vi utførte transkriptom-analyser på celler som hadde blitt stimulert med TNF-α ,et stoff som kan forårsake betennelse, og som deretter ble behandlet med RvD1n-3 DPA. En transkriptomanalyse er en metode for å undersøke hvilke gener som er aktive i en celle eller vevsprøve ved å måle mengden RNA som er produsert fra genene.

Vi fant ut at behandlingen med RvD1n-3 DPA førte til en betydelig nedregulering av gener som kan forårsake betennelse. Behandlingen førte også til at et protein ved navn P65 forflyttes ut av cellekjernen og inn i cytoplasmaet. P65 er viktig for at gener skal kunne aktiveres, og å flytte seg ut av cellekjernen kan det føre til at P65 blir ineffektiv. Siden P65 er kjent for å fremme transkripsjonen av mange pro-inflammatoriske gener, tyder dette på at RvD1n-3 DPA kan brukes for å redusere betennelse, og at det kanskje virker gjennom en ny mekanisme.

Selv om SPM-er kan hjelpe med sårheling ved å redusere betennelse, har vi fortsatt mye å lære om hvordan de påvirker bevegelsen av orale epitelceller i betennelsesmiljøer. I den tredje studien fant vi at tilsetning av RvD1n-3 DPA økte bevegelsen av orale epitelceller når de var utsatt for betennelsesmolekylet TNF-α. Vi observerte også at RvD1n-3 DPA påvirket organiseringen av et protein kalt F-aktin, som er viktig for intracellulær transport. Dette antyder at RvD1n-3 DPA kan være nyttig for å fremme helning av munnslimhinnen.

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Christine Olsen

Photo: mn.uio.no

Christine Olsen at the Department of Chemistry, Faculty of Mathematics and Natural Sciences, University of Oslo, defended the thesis "Multifaceted challenges with liquid chromatography mass spectrometry determination of bioactive hormones secreted from stem cell-derived islet organoid" for the degree of PhD, Oct. 20, 2023. The work was carried out under supervision of Professor Steven R. Wilson, Professor Emerita Elsa Lundanes, Department of Chemistry, University of Oslo and Research Scientist Frøydis Sved Skottvoll, SINTEF Digital.

Summary

Understanding islet cell biology is important for multiple metabolic diseases, including diabetes and obesity. Stem cell-derived islet organoids (SC-islets) are cell models suitable for closing existing knowledge gaps concerning glucose regulatory hormones, such as insulin, somatostatin-14, glucagon, and urocortin-3. The study aimed to obtain a highly selective, sensitive, versatile, and reliable determination of hormone secretion from SC-islets using liquid chromatography (LC) coupled with mass spectrometry (MS). The dissertation comments on the following research question: *How far can we push LC separation and MS detection of native peptides secreted from SC-islets, and what are the limiting factors?*

The dissertation found that successful determination could be obtained by tailoring the LC-MS platform toward the desired analyte and sample matrices. The limiting factors concerning LC separation of bioactive peptides were; 1) non-defined adsorption depending on column format, tubing material, and sample matrices, 2) charge state distribution of multiply charged peptides combated with MP composition, and 3) compatibility towards biologically relevant sample matrices: Krebs buffer and cell medium, requiring rugged columns and instrumental set-up. The main factor to consider when applying MS for determination of bioactive peptides was the presence of disulfide bonds, which required different sample preparation depending on the applied MS instrument.

Torstein Grønseth

Cand. Med. Torstein Grønseth at Institute of Clinical Medicine, University of Oslo, defended the thesis "Antimicrobial treatment options for Staphylococcus aureus biofilm" for the degree of PhD, Sep. 20, 2023. The work was carried out under supervision of Professor Juha Tapio Silvola, University of Oslo.

Summary

Bacterial cells can exist in a planktonic state or as part of a larger biofilm community. Biofilms are clusters of bacteria offering physical protection for the bacterial cells towards the host defense system and antibiotics.

The aims of the thesis were to assess the effect of different antimicrobial treatments on staphylococci living in biofilm, both in vivo and in vitro. In Paper 1, the antibacterial efficacy of Lugol's solution, acetic acid, and boric acid were studied. In Paper 2, the antimicrobial efficacy of Bioactive glass (BAG) on S. aureus in biofilm was studied. In addition, we assessed whether supernatant fluid primed from BAG retained its antibacterial capacity. Both Paper 1 and Paper 2 were in vitro studies. In Paper 3, the antibacterial efficacy of Lugol's solution and Gentian violet against MRSA biofilm in a murine wound model were studied.

In Paper 1 and Paper 2, three methods were used to evaluate the antimicrobial effect on S. aureus in biofilm: Biofilm-oriented antiseptic test, Bactericidal biofilm test, and Confocal laser scanning microscopy combined with LIVE/DEAD staining. In Paper 3, the antimicrobial effect on the biofilm bacteria was evaluated by measuring bioluminescence from luciferase-tagged MRSA in wounds.

In this thesis, we showed Lugol's solution to effectively eradicate S. aureus in biofilm in vitro and MRSA biofilm in vivo. Gentian violet effectively eradicated MRSA biofilm in vivo. Direct exposure to BAG granules and primed supernatant fluid effectively eradicated S. aureus in biofilm in vitro.

These findings are important since effective non-antibiotic treatments for S. aureus biofilm infections can be a supplement to, and thereby save the use of antibiotics. In addition, the low cost of the antimicrobials studied is important in a global perspective to ensure more equal access to healthcare.

Saphira Felicitas Baumgarten

M.Sc. Saphira Felicitas Baumgarten at Institute of Basic Medical Sciences, University of Oslo, defended the thesis "iPSC derived building blocks for the fat liver axis" for the degree of PhD, Oct. 13, 2023. The work was carried out under supervision of Gareth Sullivan, University of Oslo.

Summary

The number of obese adults has increased to over 300 million since 2000, affecting general health in light of the COVID pandemic and putting an immense strain on health services to cover the costs. To mitigate this will require access to effective models that allow us to understand disease aetiology, and develop novel therapeutic interventions, particularly concerning the fat-liver axis in metabolic diseases. Metabolic syndrome is complex and multifactorial and therefore not restricted to just one tissue or cell. Accordingly, we encounter the necessity of multiple cell types for in vitro modelling, since animal models are not up to the task, e.g. due to differences in cytochromes P450 enzymes of mice and humans. Thus, we are proposing minimal requirements to build an in vitro fat-liver axis by utilising induced pluripotent stem cells and their differentiation to liver organoids and adipocytes for the described application. Taken together, the results of this thesis deliver the two major building blocks to establish the fat liver axis in vitro. This could potentially facilitate the study of metabolic diseases like non-alcoholic fatty liver disease in vitro, delivering an alternative to animal models in the future.

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