OSLO UNIVERSITY HOSPITAL

Research Institute of Internal Medicine (RIIM)

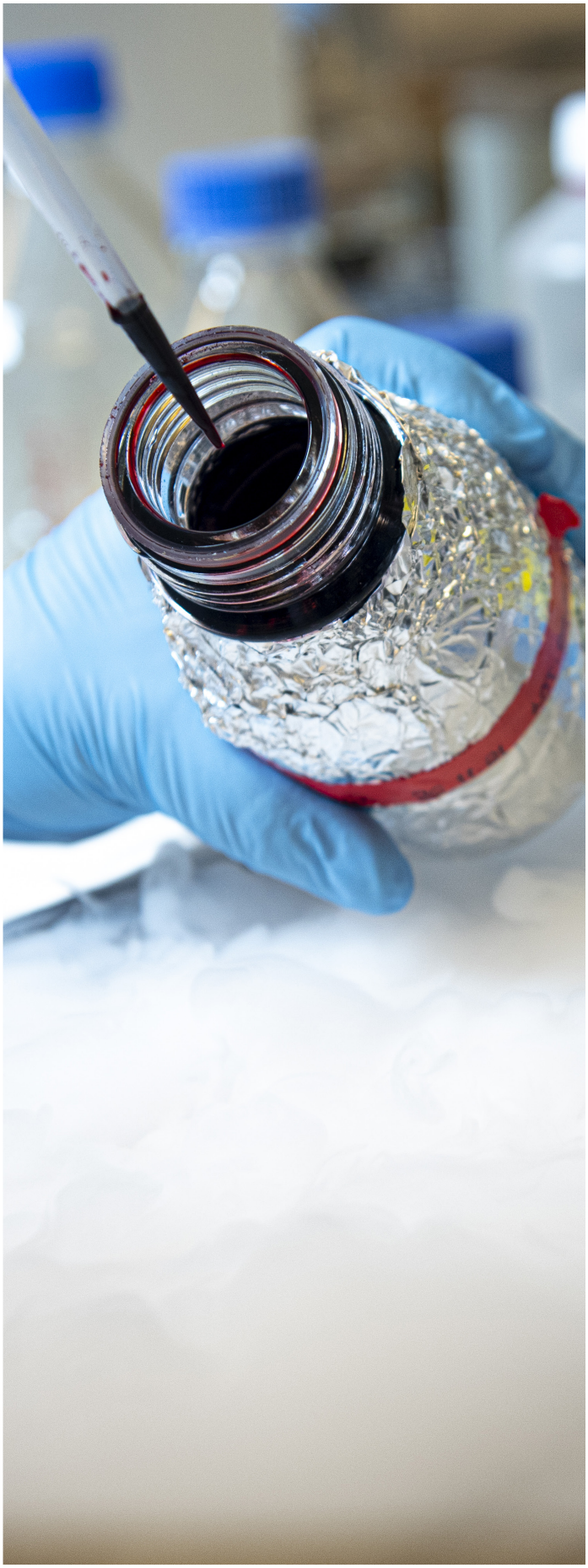
ANNUAL REPORT 2024

UNIVERSITY OF OSLO

RIIM

ANNUAL REPORT

2024



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RIIM ANNUAL REPORT 2024

More information at the web pages:
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Leader´s corner

Professor Bente Halvorsen
Head of the Research Institute of Internal Medicine

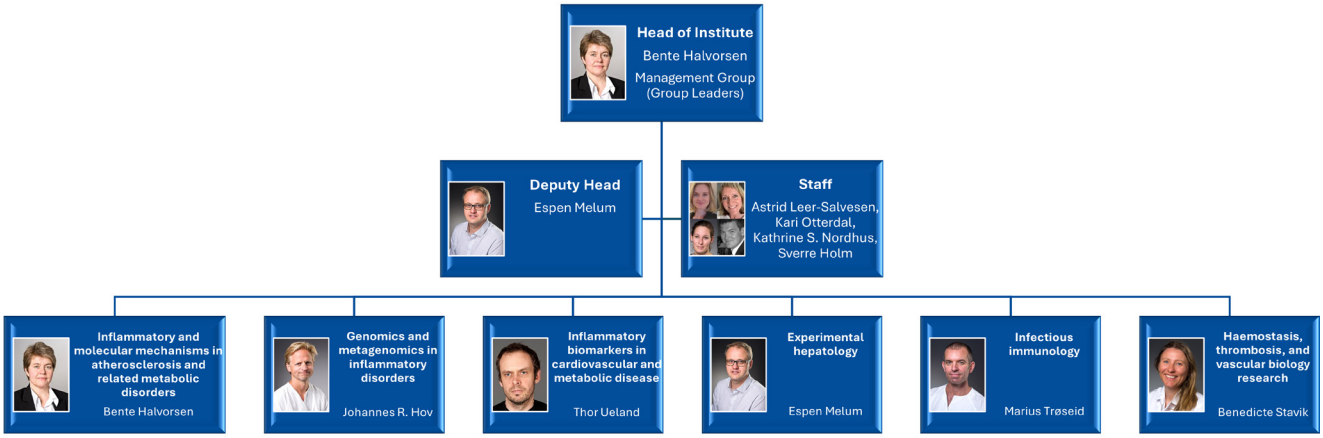
2024 was a year with large challenges but also opportunities for the Research Institute of Internal Medicine (RIIM). In January we worked hard to finalize the evaluation report to Norwegian Research Council. This was an extensive collaborative effort to collect and present RIIMs major achievements in the last 5-10 years, but also a very important work to evaluate were we stand as a translational research institute. And to encourage us to constantly perform at an excellent level.

The previous year has been colored by extensive construction work at the hospital, and planning of the moving of the Institute. This is an important task, but also demanding and detailed, including drawing of lab area, sharing of lab and office facilities between the institute, planning of how we shall/will work in a translation research lab the next 30 years. The gathering of translational research environments in the A building will be fruitful but will also come with some challenges. RIIM needs to scale down with regards to lab and office space, and that means we need to work smarter. We will need more collaboration across the different research groups at RIIM, but also with other labs outside RIIM, at UiO/ OUS, as well as national and international collaborators. I believe that the future is bright and that we, together with Institute of Experimental Medical Research, Institute for Surgical Research and Department of Pediatric Research, will step up and climb even higher in our achievements. To succeed it will require common research strategies, common meeting points and common lab equipment's and infrastructure.
2024 gave RIIM surprisingly lower external funding than previous years – a warning sign that translation research is perhaps not a strategic investment area and that the focus currently lies on clinical trials and patient-focused research. Several of the grant applications reached excellent scores, thus the competition is extremely though and will be tougher the years to come given the global situation.

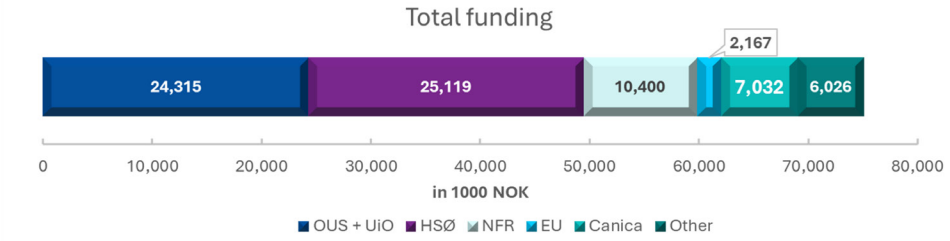
The main task as a leader in 2024 were, and will be in the years to come, to rig RIIM for the new OUS. And to focus particularly on developing RIIM`s research portfolio and pinpoint relevant grants to apply for and write excellent grant application, to achieve higher yield of external funding with a sharper research profile.

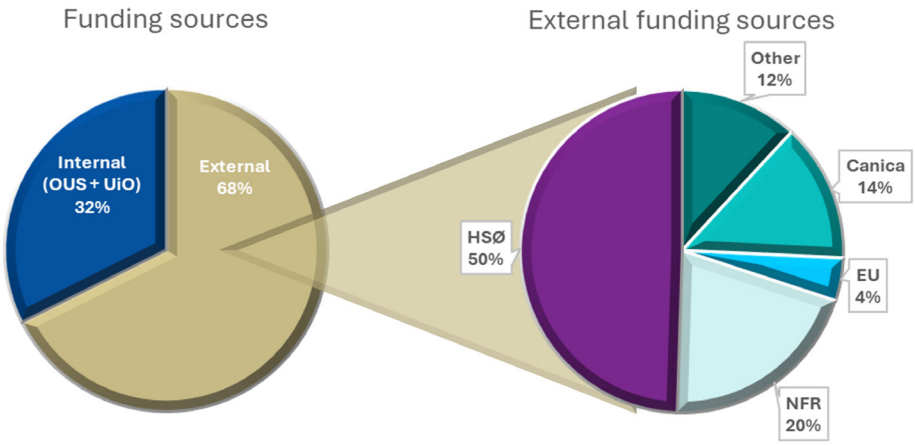
Thanks to everyone at RIIM, particularly the staff members for great work in 2024. Thanks to Turid M Pedersen who retired in 2024, after 40 years of dedication to the institute. And welcome to Astrid who has jumped into heavy duties and has taken huge responsibility in replacing Turid.

ORGANIZATION



ECONOMY / FUNDING





«The institute's total funding amounted to 75 MNOK in 2024. 50.5 MNOK (68%) was funds from external sources, while 24.3 MNOK (32%) originated from Oslo University Hospital and University of Oslo. The contributions from external funding sources are shown in the chart to the right."

FOCUS AREA

Biomarkers and Targeted Therapeutics in COVID-19 and Infectious Diseases

By Hans-Kittel Viermyr

In the treatment of infectious diseases, therapies targeting the infectious agent form the cornerstone of care. However, it is well established that a dysregulated host immune response can, in some cases, cause more harm than the pathogen itself – as seen in conditions such as sepsis and severe COVID-19. During the COVID-19 pandemic, both antiviral and anti-inflammatory therapies were extensively evaluated in randomized controlled trials (RCTs). The majority of drugs tested were repurposed; they had already been developed and approved for other conditions, providing valuable prior knowledge of both effects and side effects, although their efficacy and safety in this context remained uncertain. Ultimately, four therapeutics – one antiviral (remdesivir) and three anti-inflammatory or immunomodulating agents (corticosteroids, interleukin-6 (IL-6) receptor blockers, and the Janus kinase inhibitor baricitinib) – were shown to be effective in patients with severe disease, reducing disease progression and mortality, and were subsequently recommended in World Health Organization treatment guidelines(1).

Factors contributing to COVID-19 severity, and immune activation are complex and influenced by both viral and host factors such as genetics, age, sex, underlying conditions, vaccination and concomitant medications(2, 3). As such, immunomodulation requires careful balance – and ideally, a patient-tailored approach – as it impairs host defenses and increases the risk of secondary infections.

The complexity of human biology has long been recognized. As Sir William Osler noted in 1892, *"If it were not for the great variability among individuals, medicine might as well be a science and not an art"*. That being said, infectious disease management, particularly in the intensive care setting, is likely to benefit from – and increasingly focus on – combination strategies targeting both the pathogen and the host's immune response. Just as blood cultures are routinely taken in the emergency department to guide antimicrobial therapy, cytokine panels and other immune biomarkers may, in the future, become standard tools to guide personalized immunomodulatory treatment.

While randomized controlled trials are the gold standard for establishing treatment effects at the population level, their ability to evaluate individual variation in responses is generally more limited. The use of biobanking in RCTs during the pandemic opened possibilities to tackle this challenge. Biobanking offers the possibility to improve in-depth exploration of disease pathomechanisms and treatment effects, also at the subgroup level, which may enhance our understanding of individual variation in therapy response.

Targeted therapeutics in severe and critical COVID-19 has been a central focus of the Infectious Immunology group over the past few years. In our project, we have utilized data and biobanked material from two RCTs: the NOR-Solidarity trial (which evaluated hydroxychloroquine and remdesivir, as part of the WHO-Solidarity trial), and the Bari-SolidAct trial (which evaluated baricitinib)(4-6). The general workflow in this project is visualized in Fig. 1. The Bari-SolidAct trial was prematurely terminated before reaching the planned sample size, as sufficient evidence supporting the efficacy of baricitinib had emerged from other trials(5, 7). A unique feature of this trial, was that more than one third of the participants had been vaccinated against SARS-CoV-2, reflecting the fact that it was conducted later in the pandemic. Notably, while baricitinib appeared to reduce mortality among unvaccinated participants, consistent with findings from other trials, the opposite trend was observed in vaccinated individuals, who experienced a significantly higher incidence of serious adverse events (SAEs) when treated with baricitinib(5).

Prompted by this safety signal, a collaborative investigation was initiated, involving research groups at RIIM, the Department of Immunology, the National Centre for Viral Respiratory Infections in Lyon, France, and several other international partners. In this project, biomaterial from 146 participants – representing more than half of the total study population – was analyzed to assess nasopharyngeal viral loads, inflammatory markers in plasma, and serological responses. In addition, immune cell profiles and

mRNA expression were analyzed in a subset of participants. We explored differences between vaccinated and unvaccinated individuals as well as the effects of baricitinib on inflammation, virological and serological responses(8).
To our knowledge, this is the first study to describe the temporal effects of baricitinib on inflammatory markers and immune cell populations in the setting of severe COVID-19 within an RCT, showing its mitigating impact on soluble (s) CD25, T-cells, and monocyte-activation markers (Fig. 2a and b). Nonetheless, the effects of baricitinib were independent of vaccination status, and a mechanistic explanation for the safety signal observed in the Bari-SolidAct trial was not identified in our study(8). This is consistent with findings from a large individual participant data meta-analysis, which also did not identify a safety concern in vaccinated individuals treated with baricitinib(9).
In addition to investigating the potential interaction between SARS-CoV-2 vaccination and baricitinib treatment, this project has focused on identifying biomarkers associated with COVID-19 complications. These include biomarkers linked to the development of severe disease, complications during hospitalization, and long-term symptoms following hospitalization, including fatigue, a common debilitating symptom of long-COVID. Ideally, such biomarkers could help identify individuals at risk, support the selection of targeted treatments, and enable monitoring of treatment effects. In particular, we have identified three biomarkers that may help guide clinical decision making. First, IL-6 has been linked to disease severity and disease related complications by both our group and others (Fig. 3a and b); this cytokine can already be measured in many hospitals, and approved targeted therapies (IL-6 receptor blockers) are available(8, 10, 11). Second, we have also shown that high levels of sCD25 are associated with complications during hospitalization, and that baricitinib reduces these levels(8). Like IL-6, this biomarker is already measurable in clinical settings (as soluble interleukin-receptor, sIL-2r). Third, we have also shown that high SARS-CoV-2 plasma viral antigen levels are associated with complications during hospitalization, suggesting that this could serve as a promising biomarker of ongoing

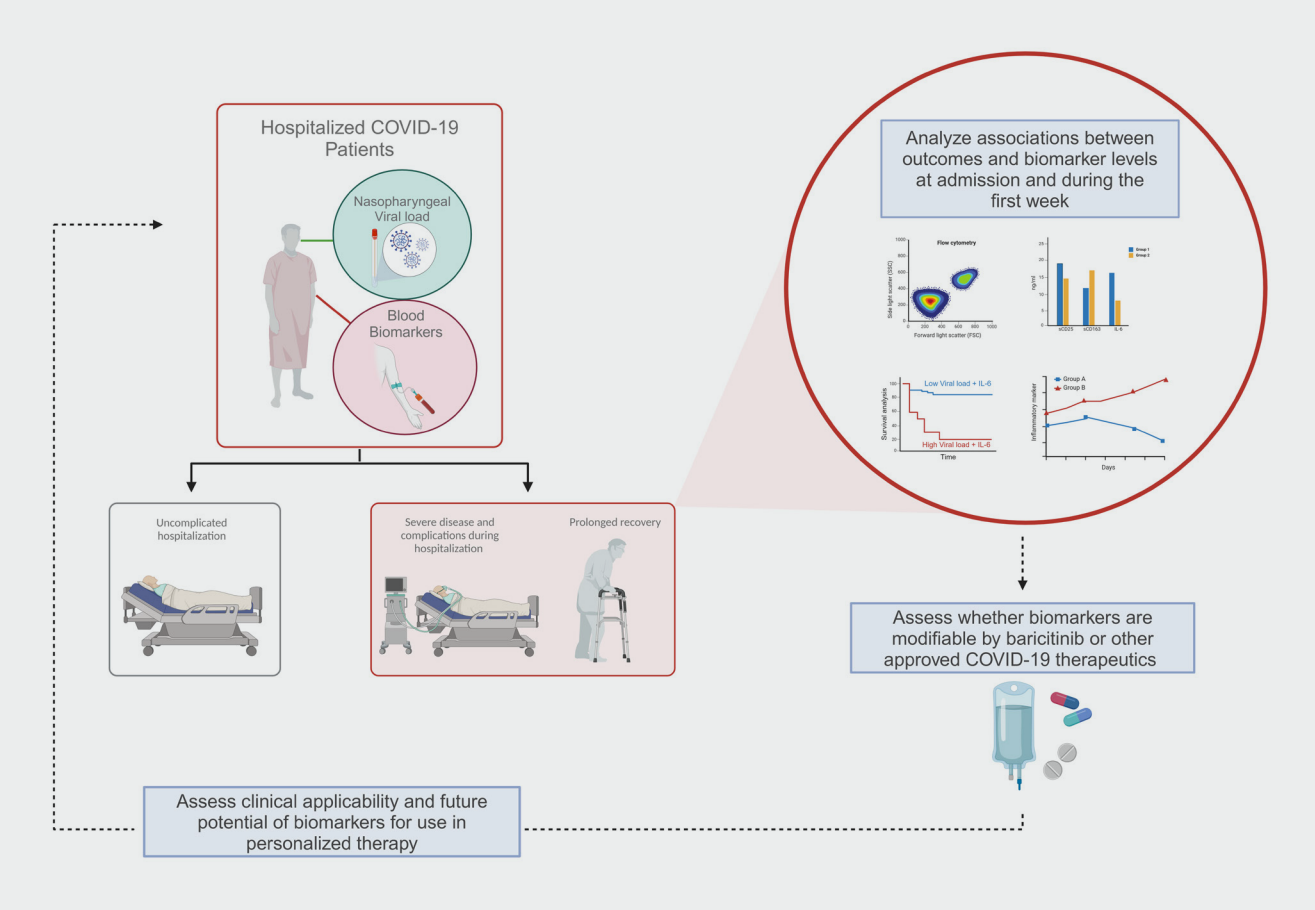


Figure 1: Overview of the analytical workflow assessing the role of biomarkers in hospitalized COVID-19 patients.

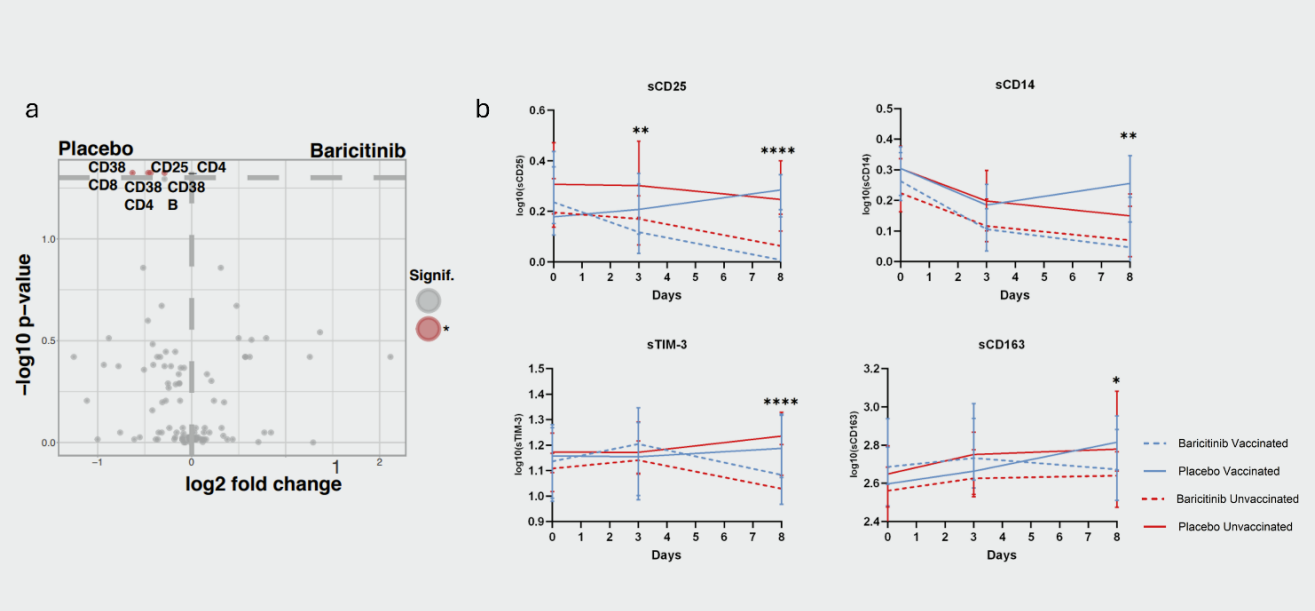


Figure 2: The effect of baricitinib on inflammation. a. Volcano plot showing cellular subsets significantly enriched in participants treated with placebo vs. baricitinib. b. Longitudinal effects of baricitinib on T-cell and monocyte activation markers, stratified according to treatment allocation and vaccination status. Red and blue lines represent unvaccinated and vaccinated patients respectively, with stipulated lines for baricitinib-treated patients, and solid lines for placebo-treated patients. Data are represented as medians and interquartile ranges (IQRs).

viremia(8). Future studies should assess whether remdesivir or other antivirals may reduce these levels, and methods for measuring viral antigen levels in routine clinical practice should be developed.

The clinical application of immunotherapies in infectious diseases currently focuses on suppressing harmful immune responses. However, other promising strategies aimed at enhancing and directing immune activity – including cellular immunotherapies – are also being explored by others as potential treatments for multidrug-resistant microbes (12). The microbiome – another focus area of both the Infectious Immunology group and other research groups at RIIM – may also offer insights that could inform future therapeutic development(13). Meanwhile, population growth, global travel, and the overuse and misuse of antimicrobials in both human medicine and agriculture

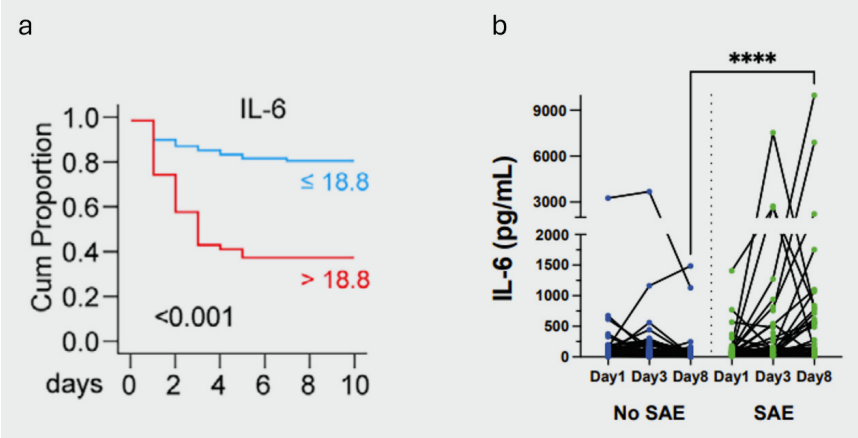


Figure 3: Interleukin-6 and severe outcomes. a. Results from the Nor-Solidarity trial, Kaplan-Meier plot showing the progression to respiratory failure and need for ICU-treatment according to low (≤18.8 pg/ml blue) and high (≥18.8 pg/ml red) admission levels of IL-6. Cut-off value determined by Youden's index. b. Results from the Bari-SolidAct trial, levels of IL-6 at admission, day 3, and day 8 in patients according to the development of serious adverse events (SAEs) during hospitalization.

are accelerating the emergence of antimicrobial resistance and increasing the likelihood of future global pandemics, highlighting the urgent need for both new therapeutics and a stronger focus on biomarkers that can help guide the right treatment to the right patient at the right time.

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Inflammation in obesity – the chicken and the egg?

By Ida Gregersen

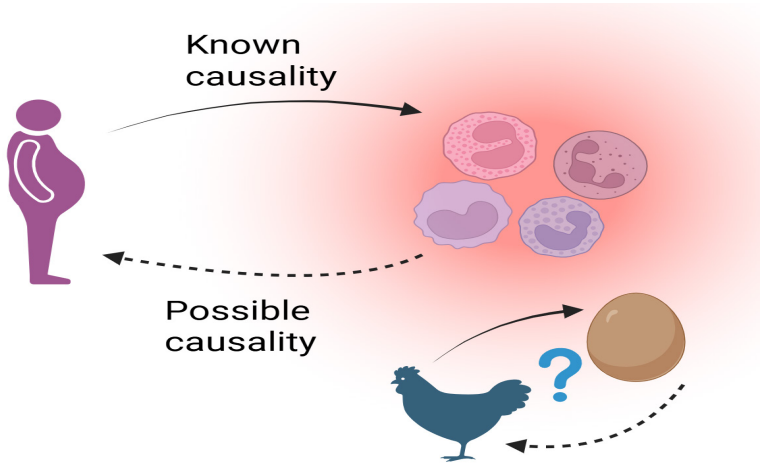
Obesity is a serious and growing health problem world-wide, resulting in major consequences for the affected individual, the health system and health economies [1]. Obesity increases the risk of metabolic disease, including type 2 diabetes and fatty liver disease, as well as several types of cancers. GLP-1R analogs have in many ways revolutionized the treatment of obesity, however these medications are costly and is not effective in all patients. There is a lot of unknowns in the pathophysiology underlying obesity, and increased knowledge is warranted to improve prevention and health care for this large and growing population.

Inflammation is a major driver of obese-related disease, however, the role of inflammation in development of obesity *per se* has traditionally not been appreciated. The last years, however, several lines of evident suggest that immune cell activation and inflammation also can be drivers of processes leading to obesity. In mice, T cells are shown to be important for weight memory and weight regain after weight loss [2]. Further, we have shown that mice with increased T cell responsiveness develop obesity, and that this

phenotype can be "transferred" to other mouse models by bone marrow transplantation and adaptive T cell transfer [3]. These novel findings suggest that inflammation, previously appreciated as "the chicken" in obesity; also, can serve as "the egg".

Obesity is a multifactorial, chronic disease, however is, in simple terms, a result of surplus energy. This is most often caused by high intake of calorie-rich food in combination with low physical activity or genetical or adaptive dysfunctional metabolism. Throughout evolution, the metabolism and immune system has been tightly connected, a relationship that in the context of obesity causes complications. Access energy will increase the demand on the metabolism and activate immune cells, leading to inflammation which, over time, can result in disease. A great capacity to store energy has in an evolutionary context been vital for survival; however, can in the modern society with high energy availability, cause severe health problems [4].

One niche that has been given growing attention in this aspect is the bone marrow, which constitute precursors of both adipocytes and immune cells. Several lines of evidence suggest a bi-directional relationship between bone marrow cell dysfunction and obesity-development. Dietary factors are shown to modulate this microenvironment [5], and these alterations has potential to impact obesity development through metabolic reprogramming of bone marrow cells [6]. Further, obesity can lead to stem cell dysfunction and which can accelerate the development of disease [7]. Activated immune cells, primed by lifestyle-related factors such as diet, can also affect adipocytes locally, and tissue macrophages are shown to regulate adipocyte reprogramming in the adipose tissue [8]; stimulating adipogenesis which can result in obesity. Thus, a continuous positive energy balance can stimulate inflammatory processes and subsequently contribute to weight gain, serving as, at least a part of, the "egg" during obesity development.



Emerging data suggest immune activation and inflammation to have a causal role in obesity development, serving as both the "the chicken" and "the egg".

There are still many uncertainties on how these processes are connected, and it is not clear how they operate in humans during obesity development. The immunity-metabolism aspect of obesity is not new, but the concept of *metaflammation as* fuel for development of obesity *per se* is novel, as well as the mechanisms underlying this. It will be an interesting research field to follow in the years to come and it might open for new therapeutic targets for this growing group of patients.

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DISSERTATIONS 2024

Photo: Ine Eriksen, UiO

Sarah Luise Mikalsen Murphy MSc

Studies of the immune response in severe COVID-19
30th of May 2024

Committee:
1. opponent: Professor Jacob Odeberg, Karolinska Institutet, Sweden
2. opponent: Researcher Markus Haug, Norwegian University of Science and Technology, Trondheim
3. opponent: Professor II Ida Gjervold Lunde, University of Oslo

Main supervisor: Tuva B. Dahl
Co-supervisor(s): Bente Halvorsen, Andreas Barratt-Due

Summary of PhD project:
COVID-19 is a deadly disease, where the most adverse patient outcomes include shortness of breath, which can devolve into complete respiratory failure. The vaccine did reduce the need for admission to intensive care units (ICU). However, still today, some patients get gravely ill without any clear answer as to why. In her doctoral thesis, Sarah L.M Murphy addressed this issue by studying the immune response in severe COVID-19 patients.
Blood samples were drawn during and after hospital admission from patients included in the NOR-Solidarity trial, which aimed to assess the antiviral effects of remdesivir (REM) in COVID-19 patients. As immune cells are key regulators of the immune response, immune cells from patients were sampled. REM had no great clinical effect on the primary outcomes. However, it was observed to be hazardous in ICU patients. Murphys analysis of immune cells revealed that REM decreased their interferon response. It might be that REM administration became hazardous by further reducing an already compromised immune response in ICU patients.
Murphy measured the expression of two chemokines, CCL19 and CCL21, in the blood samples. High admission levels of the chemokines correlated with 60-day all-cause mortality and respiratory failure. The immune cells of ICU patients showed increased enrichment of extracellular matrix (ECM) regulators. ECM remodelling is considered a vital process to facilitate infection clearance and proper wound healing. However, adverse remodelling can lead to tissue scarring. The ECM remodelling activity was visible in immune cell gene profiles and in circulation. This process was associated with severe disease outcomes, such as mortality and respiratory failure. Taken together, the Thesis conclude that an increased potential for recruitment combined with ECM remodelling and inflammation could be a driver/cause of COVID-19 severity.

Immune regulation in atherosclerosis and other cardiometabolic diseases

From left: Turid M Pedersen, Siva Krishna Vagolu, Sverre Holm, Maria Belland Olsen, Ida Gregersen, Tuva B Dahl, Øystein Sandanger, Vigdis Bjerkli, Azita Rashidi, Bente Halvorsen, Kari Otterdal, Ylva Schanke, Sarah Louise Murphy, Jonas Øgaard, Xiang Yi- Kong. In front from the top: Trine Ranheim, Camilla Huse, Helene Grannes, Ellen Margaret Lund Sagen, Astrid Leer-Salvesen, Kristina Fladseth

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About the group

Cardiovascular disease and related metabolic disorders such as diabetes, obesity and fatty liver disease are major causes of morbidity and mortality worldwide. They have many common features, such as dyslipidemia and inflammation. In our research group, we focus on immune-mediated mechanisms in these conditions. The last years we have also studied these mechanisms in Covid-19, and especially the association between Covid-19 and risk of cardiovascular disease. Further, women in cardiovascular disease has been a growing focus in our group. Women have traditionally been overlooked in cardiovascular research, resulting in underdiagnosis and undertreatment. In the common years, we will delineate the female-specific risk of myocardial infarction to improve our understanding of the underlying physiology and pathophysiology separating women and men, to improve patient care for all patients.

By exploring these processes through a translational approach, connecting basic science and the clinic, we wish to build a foundation for the development of new diagnostic and treatment targets for cardiometabolic disease. Our research group works in the cross-section between molecular biology and biochemistry, and cardiovascular, cerebrovascular, and endocrine medicine. Our ambitious goal is to delineate novel therapeutic targets and biomarkers to change clinical practice.

The group uses different research approaches, ranging from analyses of blood and tissue samples from patients to studies in genetically modified mice and cell culture systems, using advanced cellular and molecular biology. The group consists of people with different educational background and includes medical doctors, nutritionists, biochemists, bioinformatics and engineers. Such multidisciplinary competence is a great strength of our research group.

Activity in 2024

Milestones in 2024:

Poster presentation at the European Atherosclerosis Society Conference in Lyon (Fredrik A. Holme)

Scientific seminar in occasion of Professor Halvorsen`s 60th birthday

In 2024, the group had 44 publications, where group members had 15 first or last authorship.

The group runs a large span of interconnected translational projects to study the immunological and molecular mechanisms in obesity, metabolic disorders, cardiovascular disease and Covid-19, and our main projects during 2024 were:

T cells in obesity and metabolic disease. One of the main projects in the group, spanning the last 10 years, aims to decipher the role of T cells in development of obesity and metabolic disease. We study a transgenic mouse model with altered T cell activation, resulting in increased T cell responsiveness and subsequent obesity development; and is thus a unique model to explore this association. In 2024, the first paper describing this phenotype was published. Herein we present, for the first time, evidence that T cells can cause obesity development in mice; demonstrated by adoptive T cell transfer experiments and bone marrow transplantation experiment of cells from the transgenic mice to several mouse models resulting in obesity in recipient mice. The transgenic mice display increased adipose inflammation and increased T cell activation, however the mechanisms leading to obesity development is still unclear and will be an important research focus in the group for the years to come. In continuation of this paper, the group has in 2024 focused on the role of T cell activation in development of atherosclerosis, as well as more in-depth studies to further delineate the underlying mechanisms driving cardiometabolic disease in this novel mouse model.

Clinical material and add-on studies to clinical intervention trials. In addition to a wide spectrum of animal models to study cardiometabolic disease, we study molecular mechanisms in patient materials, as a bridge between the lab and the clinic. In 2024, we continued this work

and published papers describing altered immune status in patients with cardiovascular disease. We have continued to characterize the immune response of myocardial infarction patients receiving anti IL-6 treatment (in NSTEM and STEMI patients) to identify molecular mechanisms for the beneficial effects of tocilizumab in this group. Further, we have studied stroke the different signatures of atrial fibrillation stroke induced stroke compared to carotid stenosis – or cryptogenic stroke.
Further, and together with our collaborators we have in 2024 studied cardiovascular risk and inflammatory profile in several high-risk populations, including anabolic steroid users, Covid-19 patients, type 2 diabetes and familial hypercholesterolemia. For instance, in anabolic steroid users, we show that long-time use is associated with increased levels of markers of inflammation and extracellular matrix remodeling, with both hormone-dependent and a hormone-independent association with markers of myocardial dysfunction.
EU-project – Painfact. We are active partners in PainFACT, an EU-funded project investigating the neuroimmune crosstalk linking chronic pain, cardiovascular disease, and other comorbidities. Chronic pain imposes a substantial individual, economic, and societal burden, with its association to increased risk of secondary diseases further emphasizing the importance of understanding shared molecular pathways between chronic pain and comorbidities. The PainFACT consortium integrates clinical and pre-clinical data and, in 2024, presented strong evidence for associations between chronic pain conditions and increased hazard risk for cognitive, emotional, and cardio-metabolic disorders. Genome-wide association studies (GWAS) have identified potential genes responsible for these strong associations. Based on these GWAS findings, the consortium has initiated studies using genetically modified mouse models to investigate their role in linking pain sensation and cardiovascular risk.

Infectious Immunology

From left: Silje Jørgensen, Sajan Raju, Tuva B Dahl, Marius Trøseid, Xiangning Bai, Mai Fraz, Nuriye Basdag Tekin, Hanne Guldsten, Vegard Myhre.

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RESEARCH PROFILE:

The Infectious Immunology group was established at the Research institute for Internal Medicine end of 2022. The overall research focus is to characterize and understand the interplay between infections and host immunology, aiming for more targeted and personalized treatment strategies. We perform clinical translational research within Infectious diseases including COVID-19, other respiratory infections and HIV, and primary immunodeficiency including common variable immunodeficiency (CVID). This includes randomized controlled trials (RCTs) and observational studies with biobanking, with a particular focus on innate and adaptive immunity, inflammation as well as the gut microbiota. Our main patient materials are blood, airway and fecal samples, which we use for microbiome analyses, viral analyses, metabolomics, proteomics and other omics analyses, as well as inflammatory profiles and host immunology. Within our HIV and CVID projects, we also perform epigenetic and epitranscriptomic analyses of biopsies from the gastrointestinal tract. Since most of the group`s members have been recruited the last year, we are now in a consolidating phase before planning further expansion. However, a thematic expansion will be increased focus on the airway microbiota, which links previous experience from gut microbiota research with a clinical focus on airway infections as well as respiratory comorbidities within primary immunodeficiencies and people with HIV. Internationalization is also part of our strategy as several ongoing and planned projects are EU funded with possibility for young and senior researchers to visit our collaborators for shorter or longer periods of a project period. Regarding mobility, one post doc has been part time hired in an EU project lead from Madrid, and one senior researcher was recruited from Karolinska Institute in 2023, and is currently performing collaborative projects between these institutions. Funding is exclusively based on competitive funding from NRC, HSØ and EU, and the group has been successful in securing several major grants the last years.

Examples of activity in 2024:

COMicS (Copenhagen-Oslo Comorbidity and Microbiota Study in HIV infection). Planned as the largest prospective microbiome study in HIV-infected individuals. Several papers on 16s DNA microbiota data have been published. Full metagenomic sequencing data were finalized in 2024, with first manuscript submitted and several papers planned.
In collaboration with Johannes Hov group we have established the regional research network **ReMicS** (Regional research network for clinical Microbiota Science), encompassing > 25 research groups. In 2023, we hosted the 10th consecutive national microbiota meeting with around 100 participants, and in 2024, we co-hosted the first Nordic Microbiota meeting (NoMic) in Copenhagen.

We have received NRC funding for the project "**Targeting the gut heart axis**", applying integrated multi-level bioinformatics on metagenomics, metabolomics and proteomics analyses. This project resulted in novel data in 2024, showing that circulating metabolomics are to a very limited degree related to heart failure-related microbiome dysbiosis.

We have also finalized the first biobank-based studies over the EU-funded adaptive platform trial for COVID and emerging pandemics, **EU SolidAct**, set up to run phase II and phase III trials in around 15 European countries, with OUH as sponsor. Biobanked material from this unique platform study is currently being analyzed as part of the HSØ-funded **T3C** (Tailored therapeutics targeting Covid-19 in hospitalized patients) project, resulting in the first published paper in 2024.

We have also received an "Open research grant" in 2023 from HSØ on a project entitled "A new approach to disease prevention and therapy in Immunodeficiency". In this project, we will use a unique human biobank material with intestinal biopsies, blood cells, intestinal flora, diet data together with high-tech methods to study changes in DNA and RNA in intestinal biopsies and in inflammatory cells in the blood. The manuscript on **epigenetic** analyses is already submitted.

In the HSØ -funded post-doc project (HDL beyond atherosclerosis - altered **lipid metabolism** as a driver of inflammation in Common variable immunodeficiency), we have used Common variable immunodeficiency, as a model to study the role cholesterol and fat metabolism have on chronic inflammation without an increased risk of heart disease. This year we have published an article on triglyceride and VLDL-cholesterol (very low-density lipoprotein) in CVID and how increased triglyceride levels in CVID coincided with high inflammatory markers in the blood, and increased microbial imbalance in stool samples, but not heart disease.

Inflammatory Biomarkers in Cardiovascular and Metabolic disease

From left: Kristin Godang, Merisa Abusdal, Thor Ueland, Annika E Michelsen, Maren Wessel, Kari Otterdal, Tove Lekva, Monica Frøystad.

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RESEARCH PROFILE

Many disease states are associated with low-grade chronic inflammation that may result in changes in inflammatory proteins in biological fluid such as serum and plasma. Measurement of these biomarkers will therefore be useful for detecting diseases before the diagnosis and/or offer information on the mechanisms of disease and treatment targets, or be helpful in evaluating treatment responses and predicting outcomes.

A cornerstone in our research is the close collaboration with the Department of Cardiology, and evaluation of biomarkers in heart failure, acute coronary syndromes and aortic stenosis. Biomarkers reflect a wide range of inflammatory processes in the patients and can further predict adverse outcome and treatment responses.
We are evaluating the impact of systemic inflammation in pregnancy on future cardiovascular and metabolic risk. The project "Early detection of preeclampsia and future cardiovascular disease using non-coding RNA" was started in 2023 by Tove Lekva with open support grants from HSØ in collaboration with the Department of Obstetrics, Norwegian Institute of Public Health, Section of Endocrinology and the Department of Cardiology. Our hypothesis is that non-coding RNA is crucial for both development of preeclampsia and later development of cardiovascular disease. Hopefully our research will lead to an early prediction and better monitoring of this condition, in addition to possible new treatment opportunities, and more understanding of the mechanisms of non-coding RNA in the development of preeclampsia and cardiovascular disease.
The endocrine unit is a part of the research group. The main research focuses on the molecular characterization of the pituitary adenomas and finding novel biomarkers to predict the aggressiveness and recurrence, or the response to medical treatment. In addition, we carry several projects on the role of the adipose tissue and bone on the glucose metabolism and cardiovascular risk in different endocrine diseases.

Severe mental disorders like schizophrenia and bipolar disorders are major contributors of morbidity globally and is associated with both cardiovascular and cancer disease. Together with the Norwegian Centre for Mental Disorders Research (NORMENT) we have for more than 10 years analyzed levels of inflammatory molecules in circulation and demonstrated dysregulation of immune cells and endothelial cells. More recently the use of induced pluripotent stem cell (iPSC) models have enabled more mechanistic studies of how brain cells function in mental disorders.

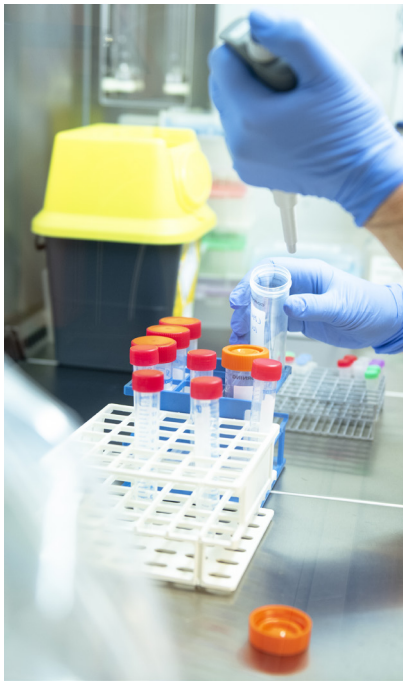
We have an ongoing strong collaboration with TREC, a translational research center at the University of Tromsø, focusing on patient-oriented and population-based research to reveal new risk factors and mechanisms for the formation of venous thrombosis.

In addition, we have strong collaborations with other clinical research, national and international projects.

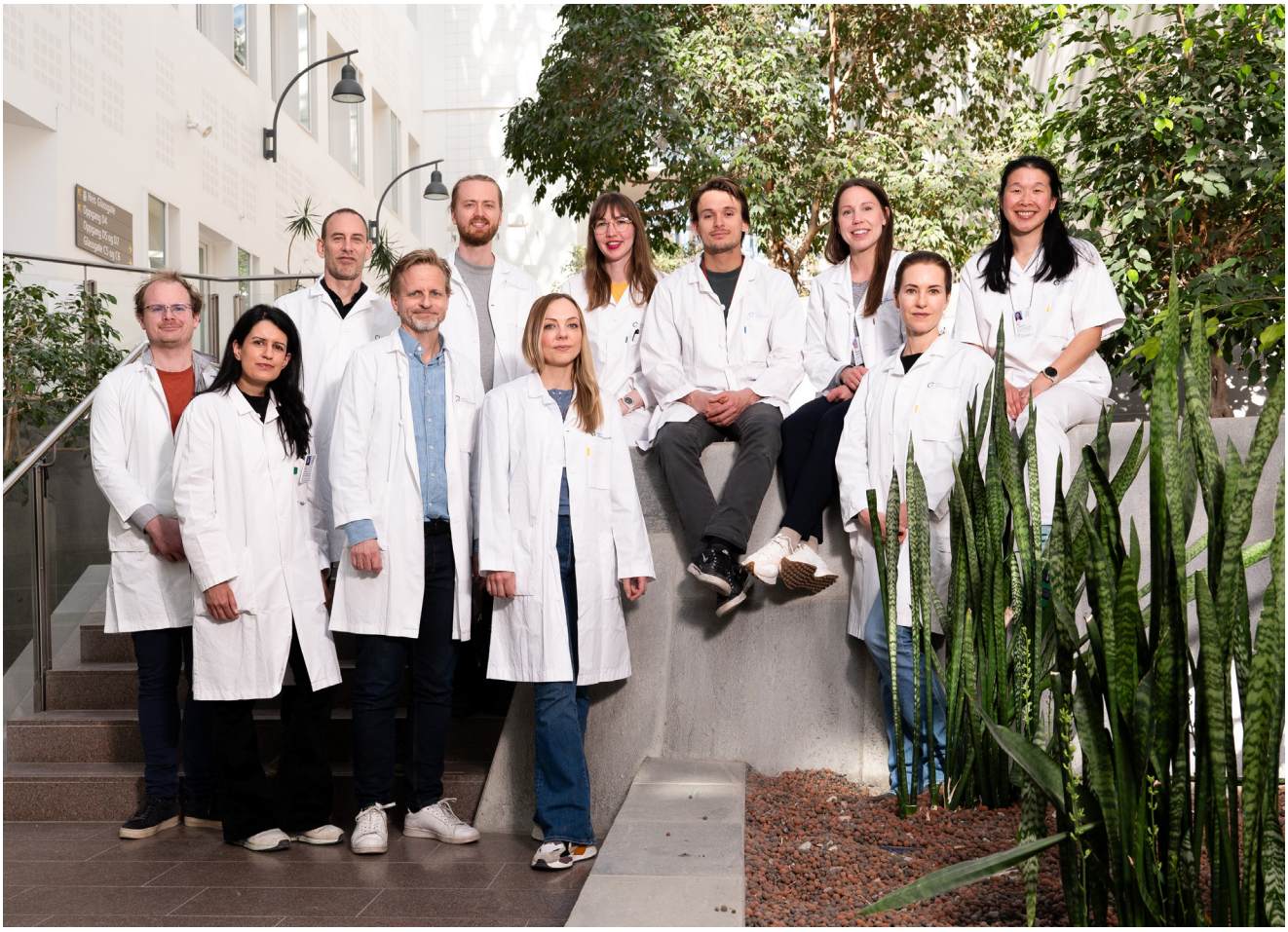
EXAMPLES OF ACTIVITY IN 2024

1. The inclusion of patients for the HSØ project "Early detection of preeclampsia and future cardiovascular disease using non-coding RNA" with grants from the Southern and Eastern Norway Regional Health Authority was started in 2024 and has been completed now (April 2025). In this study, blood samples including PBMC, and placental tissue has been collected from pregnant women at term. We have sorted immune cells and trophoblast from women with normal pregnancy and pre-eclampsia. Next steps RNAseq of non-coding and coding RNA in these cell populations.

2. We have started the HSØ project "Use of omics technologies to identify biomarkers and treatment targets in ACS". In the initial part of this project we seek to identify markers that can predict long-term adverse outcomes in patients with STEMI and NT-SEMI. In the discovery study, an aptamer based proteomic screen (SOMAscan) was performed on 100 patients, half survivors and half non-survivors. Bioinformatic analysis has been performed and we have established validation assays for 14 proteins we will evaluate in a population of 2500 STEMI and NSTEMI patients and assess their predictive capacity.



Genomics and metagenomics in inflammatory diseases



Simen Hyll-Hansen, Kristin Holm, Peder Braadland, Petra Hanzely, Jørgen Rønneberg, Sara Tjønnfjord and Hanne Lyche Alme. Front: Isma Sohail, Johannes Hov, Beate Vestad and Hanne Guldsten.
Photo: Åsne Rambøl Hillestad, UiO

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RESEARCH PROFILE

The genomics and metagenomics group aim to characterize and understand how the human genome and the gut microbiome influence inflammatory disease, and how this knowledge can be applied clinically. Our general approach is to use unbiased discovery tools like nontargeted high-throughput omics (e.g. sequencing and metabolomics), followed by targeted hypothesis-driven methods, supported by bioinformatics and biostatistics including machine-learning. We also use gnotobiotic and conventional mouse models for in vivo discovery and validation purposes, as well as advanced in vitro/ex vivo models (organoid systems), to define cause-or-effect and disease mechanisms.
Our main interest is primary sclerosing cholangitis, a disease of the bile ducts of the liver, but we are also involved in research in multiple other conditions relevant for the institute. Our main human materials are blood and fecal samples, while our experimental agenda involves germ-free and conventional mice with and without inflammatory biliary or intestinal disease, as well as organoids, in collaboration with the Melum group.

Our current main working hypothesis is that biochemical footprints of microbial activity is driving disease. We aim to define altered functional microbial changes using metagenome sequencing (i.e. the study of all microbial genes) and metabolomics. Our first interesting finding was of altered microbial metabolism of essential nutrients is altered in PSC, with deficiency of vitamin B6 as a potential disease-modifying factor caused by microbiome changes. A clinical trial focusing on translational aspects of vitamin B6 supplementation is ongoing and aims to complete recruitment in 2025 (Pyridoxine in primary sclerosing cholangitis, PiPSC). This represents an example on how we work to identify and potential treat altered microbial functions, defining their clinical impact as biomarkers or in therapy. We are applying this methodology also on recurrence of PSC after liver transplantation, which is a significant clinical problem.
With growing data size and complexity, we increasingly depend on bioinformatics and statistics. In our IBD focused projects, now comprising thousands of samples, in collaboration with the Inflammatory Bowel Disease in South-Eastern Norway 3 study, we now apply more advanced bioinformatics and artificial intelligence to improve the yield from big data from microbiome or metabolome analyses.

The groups also work more disease independent with *Clinical microbiota medicine*, as part of a Strategic research area at Oslo University Hospital funded from 2019-2024. In 2023 and 2024, one important focus was to increase the activity and capacity of the donor bank for fecal microbiota transplants. Finally, following ten years of annual National Microbiota conferences in Norway, the first Nordic Microbitoa conference was successfully organized in Copenhagen in

2024 and will onwards remain a Nordic event.

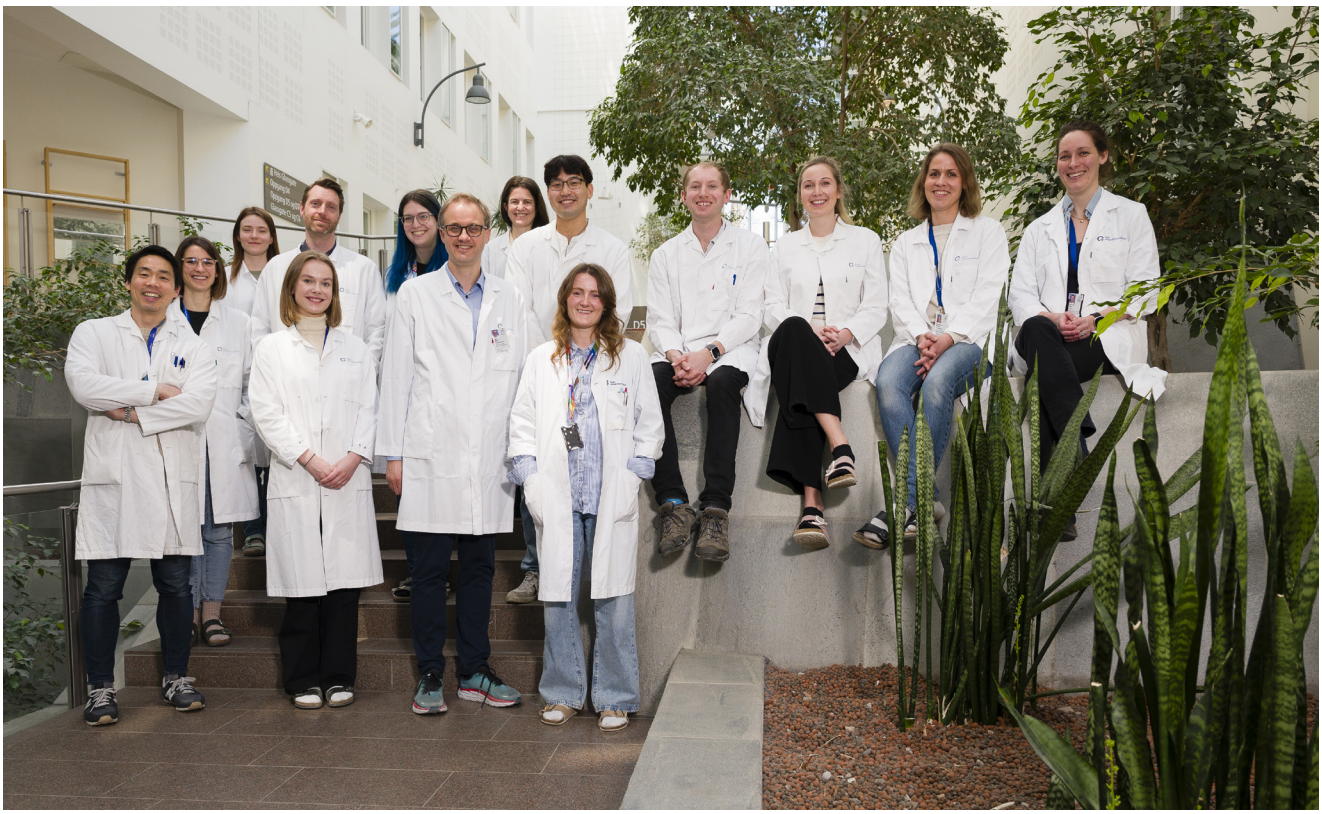
FUNDING

The group leader was awarded an ERC Consolidator grant at the end of 2024 to the project “FatVersusBile”, which will be very important in the group activities until 2030. In addition, the group is funded by multiple grants from the Regional Health Authorities of South-Eastern Norway, as well as Canica.

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

Locally, the group has extensive collaborations ongoing within NoPSC and the Research Institute of Internal Medicine, multiple clinical research groups (including in particular the IBD group at the Ullevål campus) as well as pathology and radiology. Regionally and nationally, the group has been working in the ReMicS network (Regional research network for clinical Microbiota Science), with Hanne Guldsten as administrator.
Internationally, we have strong collaborations both within and outside the International PSC Study Group, with the currently strongest links to Swedish groups in Stockholm, Gothenburg and Uppsala, in addition to US group (Brigham, Mayo clinic) and Germany (Kiel).

The Experimental liver research group



From back left; Brian Chung, Sarah Peisl, Lisa Brynjulfsen, Jonas Øgaard, Marie-Christin Röcklinger, Elisabeth Schrumpf, Jeremy (Wen Jie) Yeoh, Henry W. Hoyle, Anna Frank, Oda Ramberg and Kathrine Nordhus
Front: Oline Hovland, Espen Melum and Enya Amundsen-Isaksen
Foto: Øystein Horgmo, UiO

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RESEARCH PROFILE

The experimental liver research group focuses on experimental and translational studies related to primary sclerosing cholangitis (PSC). Our laboratory activities take place at the Research institute of Internal Medicine. In 2024 the group consisted of the group leader, four senior researchers, four postdocs, four PhD students, the lab manager, one researcher and two technicians. The overarching topic in the group is to understand mechanisms regulating cholangitis with a clear focus on immunology and the interaction of the immune system with the microbiome and the role of cholangiocytes in propagation of inflammatory processes. A key aspect is to establish new methods for characterizing and modelling PSC.

Our strong collaboration with the Hybrid-technology-hub on the bile-duct-on-a-chip is crucial for the project-team working on the chip. As part of our participation in the University of Oslo's SPARK program for commercialization we further develop the innovative aspect of the chip and submitted a patent for the original design which we now call version 1 of the chip. In parallel with this we develop version 2 of the chip where we will integrate the immune system. This task will be central for Dr. Wen Jie (Jeremy) Yeoh who joined the group as a postdoc in October 2024. Jeremy received his masters from Imperial College in London and then trained in immunology at the University of Bern where he defended his PhD thesis giving him an ideal background for taking on this task.

Our collaboration with Novartis in Basel continued in 2024 and the team was strengthened with the recruitment of Dr. Marie-Christin Röcklinger who will have the main responsibility for conducting the drug-screen in Basel and the follow-up functional experiments in Oslo. Prior to joining NoPSC Marie finished her masters and PhD in Vienna where she worked on developmental biology. Access to healthy tissue for research is important and organoid technology open up new opportunities for propagating collected tissue. After approval from the regional ethics committee, we have started to generate organoids from organ donors. This was made possible by an institutional grant for biobanks that enabled us to hire Oline Øie Hovland who established our 'Living biobank' in 2024.

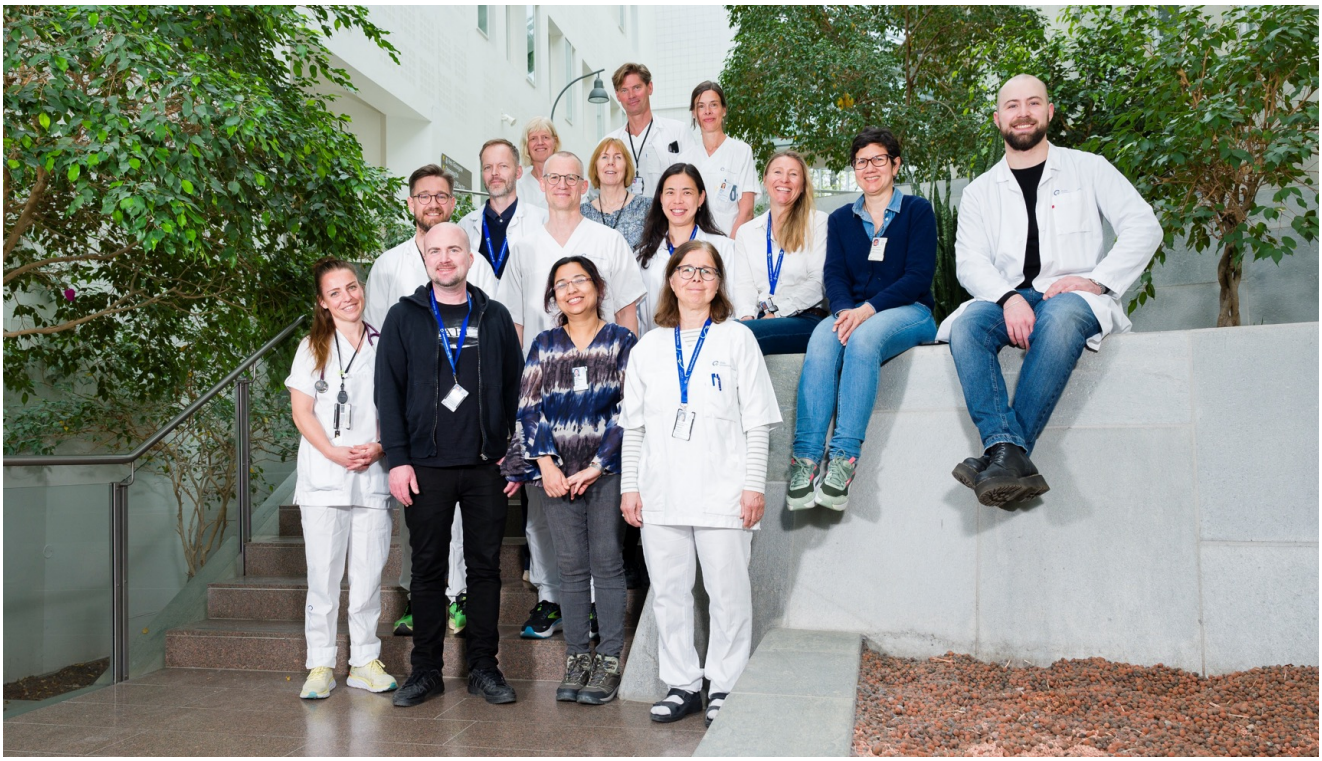
In our joint project with the Seoul National University, SINTEF and OsloMet that was funded through the National Research Foundation of Korea we had one workshop in Seoul, Korea and a project meeting in Oslo. Based on this collaboration a tool evaluating the PSC literature using artificial intelligence has been developed. In the CD100 project we have, based on our previous finding that the CD100 mutation contributes to pathogenic Th17 differentiation at the cholangiocyte-immune interface, performed targeted analysis of known Th17-driving factors that unexpectedly revealed strong additional pathogenic concepts, highlighting potential novel tissue-specific targets for treating biliary inflammation in PSC.

The group also completed several projects using spatial transcriptomics and single-cell sequencing to characterize human and murine bile duct inflammation in 2024. Papers based on two of these projects were submitted towards the end of 2024. Three additional projects were presented at the EASL congress as abstracts and final additional analyses were completed in 2024. The process of recruiting a new postdoc who will extend these findings and integrate the multiomic datasets with protein based data was started towards the end of the year.

In 2024 we published two papers using germ-free mice and we started the process of developing the gnotobiotic mouse facility further in collaboration our close partner Henrik Rasmussen who is heading the OUS animal facility and the group of Johannes Hov at NoPSC. The next years will include a significant expansion in terms of technical equipment that will enable us to perform more advanced projects.

After consistently demonstrating a functional loss of CD1d on cholangiocytes from mice with a conditional deletion of CD1d in the bile ducts using organoid technology we were in 2024 able to in-detail characterize the role of CD1d on the biliary epithelium in vivo. This was done both in the setting of cholestasis using the bile duct ligation technique and antigen driven natural killer T-cell activation by injecting oxazolone.

Haemostasis, Thrombosis, and Vascular Biology Research



In front, from left: Malu Katalina Marie Lian Hestdalen, Knut Husø Lauritzen, Anindita Bhattacharya, Marie-Christine Raymonde Mowinckel. Second row, from left: Trym Døviken, Jørn Dehli Kristiansen, Xue Yan Cui, Benedicte Stavik, Maria Eugenia Chollet Dugarte, Giacomo Roman. Third row, from left: Christian Qvigstad, Britt Jakobsen. Back row, from left: Marianne Seierstad Andresen, Pål André Holme, Ragnhild Johanne Måseide.

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We conduct basic, translational, and clinical research within the field of haematology. Last year, two new PhD students started their up their projects, we got admitted to the SPARK Norway innovation programme, important project milestones were reached, and…. The research group has two areas of interest within haematolgy, one lead by Stavik and Sandset, and one lead by Holme.

RESEARCH PROFILE Sandset/Stavik:

"Coagulation Factors: Role in the Development of Thrombosis, Inflammation and Cancer"

We study the pathophysiological role of blood coagulation proteins in thrombosis and haemorrhage, but also in other pathologic conditions such as inflammation and cancer. Our main goal is to identify how and why components of the blood coagulation process contribute to disease development, and to utilize this knowledge to improve patient care.

Activity in 2024:

Inherited coagulation disorders – ex vivo liver cell models and cell therapy

Inherited deficiency in coagulation proteins can cause mild to severe bleeding or thrombosis in affected individuals. The deficiency is caused by a mutation in the corresponding gene that results in reduced or diminished activity of the protein in plasma. Most coagulation proteins are produced in the liver and secreted to plasma and, with help from our collaborator Gareth Sullivan, we utilize stem cell technology to generate patient-derived liver organoids in the lab, to model coagulation protein production and secretion. In 2024, we successfully produced gene edited, patient-derived liver organoids that showed increased secretion of the missing coagulation factor. The project was admitted to the SPARK Norway innovation programme, and with the help of an experienced and talented coordinator and mentor, we are identifying and addressing important steps toward clinical testing of the organoids in humans. In parallel, we have identified the most optimal method for transplanting the organoids into mice.

Bone marrow microenvironment in Multiple Myeloma

Multiple myeloma (MM) is a B cell malignancy where abnormal plasma cells accumulate in the bone marrow. These patients are prone to cancer-related thrombosis already at the precursor stages of the disease and we are deciphering the tumour microenvironment for possible explanations using single cell sequencing. Last year, 8 new samples were sequenced at the genomic core facility at OUS and with the help of a bioinformatician, we are now analysing the data.

Drug repurposing

Drug repurposing has become a valuable tool to find new treatments to various diseases with low cost and little time. Previous findings in our lab indicated that an approved drug was able to increase the activity of mutated FVII. We therefore performed a larger screen using >1000 FDA approved drugs to identify potential compounds. The screen identified two hits, and last year we finalized the last experiments verifying the effects of the hits in a cellular system. The work is anticipated to be submitted for publication in January 2025.

Coagulation proteins in atherosclerotic disease

Atherosclerosis is an inflammatory disease that culminates in thrombotic complications. Using a biobank of human carotid plaques, we are looking into the presence of coagulation factors inside the plaque and investigate their potential role in regulating inflammation and plaque development. The aim is to identify regulatory targets that can reduce the inflammatory burden and, potentially, be beneficial in attenuating atherothrombosis.

Biobanking

Our general biobank for thrombosis and hemostasis research is growing and we have now collected samples from >150 patients with bleeding or thrombosis for future research. The bank now contains samples from both congenital and acquired haemophilia patients. The accompanying registry was approved by the hospital data protection officer in 2024, and work has begun setting up the registry.

RESEARCH PROFILE Holme:

"Haemostasis and Bleeding Disorders"

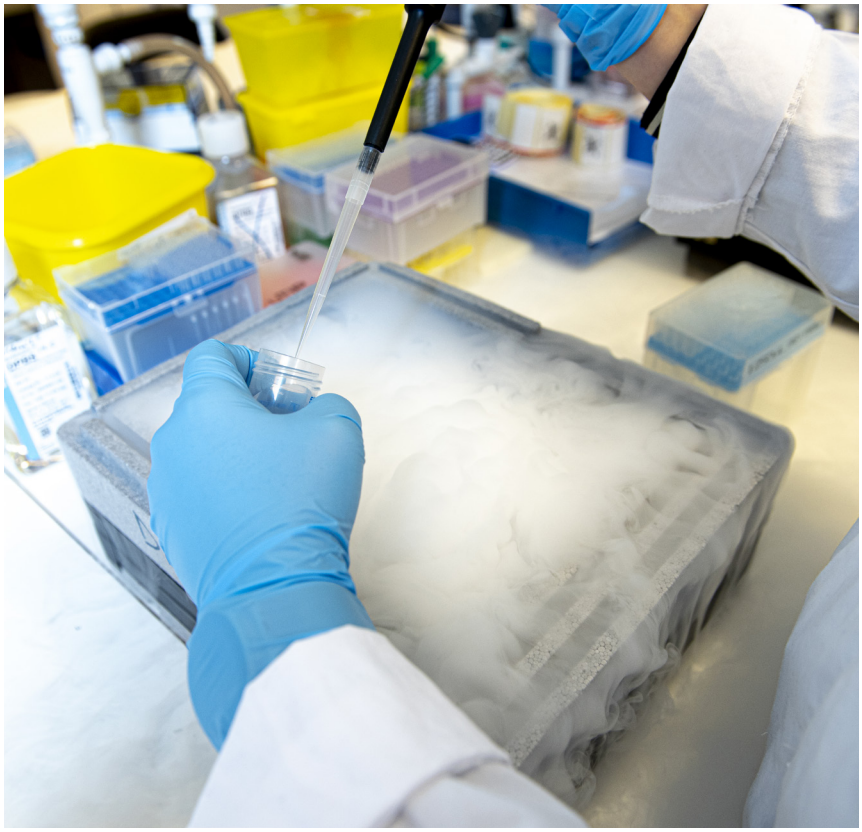
Our scientific interests are focused on clinical and basic aspects of normal and disturbed haemostasis

in particular bleeding disorders like hereditary and acquired coagulation disorders.
Oslo University hospital, Rikshospitalet is the only Haemophilia Comprehensive Care Centre in Norway and is one of the biggest haemophilia centres in the Nordic region taking care of more than 1200 persons with bleeding disorders. Several research projects are ongoing besides clinical activity.

Investigator initiated activity in 2024:
VITT- Vaccine-induced immune thrombotic thrombocytopenia
From March 2021 the group has worked extensively on the SARS-CoV-2 vaccination-related thrombotic complications and thrombocytopenia giving devastating adverse events. This has been done in close collaboration with other groups here at RIIM and Department of immunology, OUS and the Norwegian National Unit for Platelet Immunology, Division of Diagnostics, University Hospital of North Norway. This work lead to the first main publications: Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021;384: 2124-30 and Immune Complexes, Innate immunity, and NETosis in ChadOx1 vaccine-induced thrombocytopenia. Eur Heart J. 2021; 42:4064-72. Further work on this and thrombosis associated with SARS-CoV-2 vaccination is ongoing to study causal relationships including mRNA SARS-CoV-2 vaccines.

MOHEM-1 and 2– Moderate Haemophilia A and B in the Nordic countries
In the MOHEM-1 study the current joint health in moderate hemophilia A and B was described and the role of global coagulation assays was explored. The findings were published in 2020-2021 and suggested that primary prophylaxis should be administered to all patients with factor levels ≤3 UI/dL and that thrombin generation may assist in predicting bleeding phenotype in these patients.
In MOHEM-2, PhD student Malu Hestdalen is investigating pharmacokinetic properties of extended half-life FactorVIII and FIX in persons with moderate hemophilia, aiming to find a parameter as a potential tool for personalizing treatment.

IPA – Immunological Profile in Acquired disorders of hemostasis
From February 2024 the group has been working to identify the immunological profile of acquired hemophilia A (AHA), immune mediated thrombotic thrombocytopenia purpura (iTTP), refractory immune thrombocytopenia (rITP) and catastrophic antiphospholipid syndrome (CAPS). Proteomics and flowcytometry. Clinical features, response to treatment, coagulation status will be investigated in addition to activation state and phenotype of immune cells and immunological markers. This is a collaboration with Professor Ludvig Munthe and the Department of Immunology and PhD student Trym Døviken is carrying out the project.
AVA - The study of Anticoagulation with apixaban in patients with Venous vascular Anomalies
Vascular anomalies are congenital defects of vasculature which may be invalidizing and painful and have few therapeutic options. It is associated with intravascular coagulopathy, with local thrombus formation and an increased general bleeding tendency. PhD student Puneet Kaur started in February 2025 with a project investigating the effect of anticoagulation with apixaban on pain and coagulopathy and studying coagulation parameters, platelet function, endothelial marker and inflammation in this patient group.



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Forskerne oppdaget at fedmen kunne «overføres» fra én mus til en annen gjennom immuncellene. (Foto: Tuva B. Dahl)

Overraskende funn hos mus gir ny kunnskap om fedme

En endring i genene førte til at musene plutselig ble overvektige. Forskerne kunne videre «overføre» fedmen fra disse musene til friske mus. – Det er ganske stilig! sier forsker Ida Gregersen.

Elin Martine Doeland, KOMMUNIKASJONSRÅDGIVER — Universitetet i Oslo

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Overvekt og fedme er et stort folkehelseproblem, både i Norge og i verden. I dag har én av fem voksne i Norge fedme. Det vil si at de har en kroppsmasseindeks, såkalt BMI, på 30 eller mer.

I dag vet vi mye om hva som ligger bak utviklingen av fedme. En usunn livsstil med høyt inntak av kalorier og lite fysisk aktivitet gir økt lagring av fett i kroppen. Det igjen øker vekten.

Likevel er det mye vi ikke vet om de underliggende mekanismene. Hva skjer i kroppen på molekylært nivå?

Forskere ved Universitetet i Oslo og Oslo universitetssykehus (OUS) gjorde nylig en uventet oppdagelse på mus. Den gir ny innsikt i noe av det som kan ligge bak utviklingen av fedme.

– En genetisk endring gjorde at alle musene spontant ble overvektige. Det var helt uventet, forteller forsker Ida Gregersen.

En forandring i genene gjorde musene overvektige

Musene som Gregersen og kollegene hennes forsket på, hadde en genetisk endring i en type immunceller kalt T-celler. Den genetiske endringen gjør at disse immuncellene blir mer aktivert enn hos vanlige mus.

Musemodellen var utviklet av en gruppe forskere ledet av professor Kjetil Taskén. Opprinnelig skulle de forske på HIV, der T-cellene spiller en viktig rolle.

– Den genetiske endringen gjorde at musene ble spontant overvektige, uten at de hadde endret kosthold eller ble påvirket på en annen måte, forklarer Gregersen.

– Fedmen var en slags bivirkning av den genetiske endringen, legger hun til.

Kunne «overføre» fedme fra én mus til en annen

Forskerne bestemte seg for å finne ut av hvorfor disse musene utviklet fedme. Var det virkelig immuncellene som lå bak?

Musene som Ida Gregersen og kollegene hennes forsket på hadde en genetisk endring i en type immunceller kalt T-celler. (Foto: Øystein H. Hansen / UiO)

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I en podcast-serie på tre episoder gir Labprat en grundig gjennomgang av hvordan de revolusjonerende slankemedikamentene virker (Foto: Hollie Adams, Reuters, NTB)

Slik virker de revolusjonerende slankemedisinene

PODCAST: Ozempic og Wegovy ble laget for å behandle diabetes, men de gjør også at folk går ned i vekt. I tillegg kan de hjelpe mot alt fra lakoholmisbruk til Alzheimer. Hvordan virker egentlig disse medisinene?

Xiang Yi Kong, PODCASTER — Ida Gregersen, PODCASTER — Marie Belland Olsen, PODCASTER

PUBLISERT 29.11.2024 • 00:01

Labprat

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En podcast der Xiang, Maria og Ida gir deg en god blanding av fag og fjas om forskerlivet!Laget av tre forskere fra Institutt for Indremedisinsk Forskning ved Oslo Universitetssykehus, Rikshospitalet og Institut MORE

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«13 new episodes of our popular podcast «Labprat» were released in 2024, and Maria Belland Olson, Ida Gregersen and Xiang Yi Kong continue to invite local and external guests to discuss everything from AI in research, aging and extreme weight loss. Look for it on your podcast platform or https://podcasts.apple.com/no/podcast/labprat/id1579682363."

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