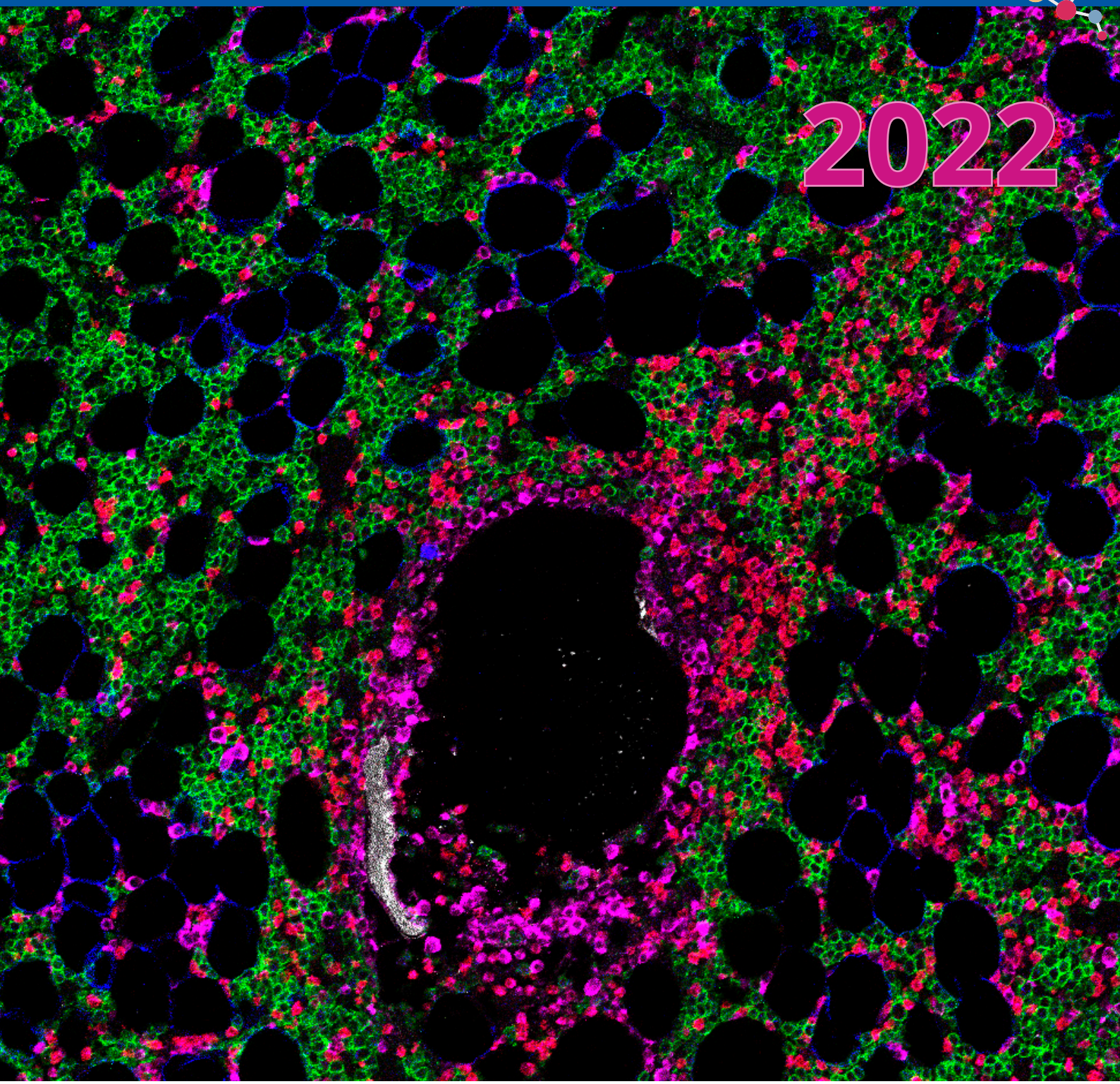
2022



Norwegian Centre of Excellence

The Research Council of Norway

CEMIR

Centre of Molecular Inflammation Research

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Page 1: Imaging mass cytometry of a section from a bone marrow biopsy obtained from a patient with multiple myeloma. The section is stained with antibodies conjugated to heavy metal isotopes and analyzed by time-of-flight in a mass cytometer. Myeloma cells are visualized in green (anti-CD138), neutrophils in magenta (anti-myeloperoxidase), adipocytes in blue (anti-perilipin), hypoxia-inducible factor 1-alpha in red and collagen type I in white. Photo: Ingrid Aass Roseth.

Director's comment

The vision of CEMIR is to find out how sensors in the innate immune system initiate and regulate inflammatory responses. This new knowledge will be used in disease models to identify new therapeutic targets and diagnostic tools for inflammatory diseases.

CEMIR unites scientists across disciplines to get detailed insight in basic biological- and clinical inflammation research. The CEMIR research activities are located in the Knowledge Centre at Øya Campus in Trondheim, which hosts first-class laboratories with state-of-the-art cellular imaging instruments. We have a BSL3-laboratory, offering the highest level of security for research on viruses and bacteria in Norway. The new lab contains an advanced Leica SP8 confocal microscope making it possible to study infections in immune cells with viable mycobacteria and HIV virus.

By the end of 2022 56 scientific staff members, 13 technicians, 16 students and an administrative coordinator were associated with the Centre. The funding from the RCN to the Center will expire by the end of 2023. As a result, several of our best researchers have left to seek more secure positions elsewhere. This is very unfortunate, however, CEMIR is now a formal research unit in the Department of Clinical and Molecular medicine. This will hopefully help us in securing some sort of continuation of the Centre beyond 2023.

The scientific activities at CEMIR have proceeded with very good progress. In 2022 68 papers have been published. CEMIR researchers have published a total of 600 articles since the start in 2013, several in high quality journals like Nature Communications, Blood, Science Advances, Science Immunology, Plos Pathogens, Cell, Science, Nature, Nature Immunology, Autophagy, J Cell Biol and PNAS. 42 CEMIR PhD candidates have successfully completed their PhDs. Several of the publications from CEMIR have received front page coverage in journals such as PNAS, Traffic, Nature Immunology, Science Immunology and J Immunol. The high quality of the research is also illustrated by the fact that the Center received evaluation as exceptional by an international evaluation committee in 2017.

Research at CEMIR has also resulted in innovation and submission of a PCT patent application in 2021. We have discovered that peptides from an immunoreceptor are able to inhibit inflammatory responses in macrophages. These peptides have the potential to be developed into novel drugs for treatment of pathological inflammation.

In 2022, professor Tom Eirik Mollnes, who is affiliated with CEMIR received the gold medal from the European Complement Network for excellent research on complement in Europa. Mollnes was also appointed as honorary doctor at Copenhagen University. Professor Harald Stenmark, who is also affiliated with CEMIR, received in 2022 Anders Jahres medical price. Congratulations to both.

CEMIR has a strong focus on basic innate immunity and how it relates to human inflammatory diseases. Research from CEMIR has given new knowledge about mechanisms and new targets for treating inflammatory diseases like infections and cardiovascular diseases. This has helped us in achieving the primary goal to identify new therapeutic targets and diagnostic tools for inflammatory diseases. In order to show the impact of our research, it has been a priority for the Centre to further strengthen the collaboration with clinical departments at St. Olav's Hospital.

Terje Espevik

Terje Espevik
Centre director

Cemir Research Themes

Theme 1: **Intracellular Trafficking and Compartmentalized Signalling**

Theme Manager: Professor Terje Espevik

Microbes induce trafficking pathways that are important for activation, inactivation or evasion of Toll-like receptors (TLRs) and inflammasomes. TLRs in macrophages initiate different destruction programs depending on the particular microbe encountered. TLR signalling proceeds through adapter pair molecules like MyD88-MAL- and TRAM-TRIF. NLRP3 inflammasome activation results in maturation of IL-1β and in pyroptosis. Despite the large amount of research, we still do not know much about the cell biological mechanisms on how TLRs and inflammasomes control killing of bacteria.

We have pinpointed new important players in phagosomal signalling that are required for killing of Gram-negative and Gram-positive bacteria. One of them is Rab11-family interacting protein 2 (Rab11-FIP2) that we now have shown to play a master role in pyroptosis.

The other is SLAMF1 which modulates macrophage responses to microbes in mice. SLAMF1 is an Ig-like receptor and a costimulatory molecule that initiates signal transduction networks in a variety of immune cells. We have discovered that SLAMF1 is potent regulator of TLR signalling in human macrophages, a finding that have suggested new therapeutic targets. We also have a research focus on the combined effects of complement and TLRs in phagocytosis and host defence against bacteria. In Theme 1, we aim to obtain mechanistic understanding for inflammatory signalling, and use this information to find new therapeutic targets to treat pathological inflammation.

Main activities 2022

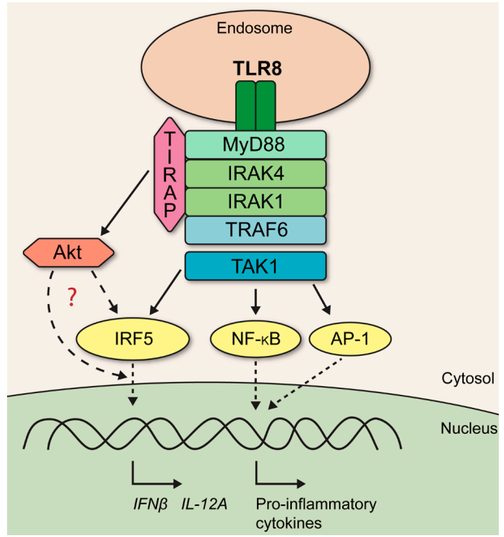
Pyroptosis is a type of cell death that causes a high level of inflammation that is triggered by bacterial infections. We have studied the role of Rab11-FIP2 and other Rab11 interacting proteins in the regulation of LPS stimulated NLRP3 inflammasome activation. In contrast to other Rab11-FIPs, Rab11-FIP2 was found to play a master role in the controls of pyroptosis. We have found that Rab11-FIP2 stabilizes NLRP3 and pro-IL-1β at the protein level. Also, that Rab11-FIP2 controls the translocation of NLRP3 to the trans-Golgi network where activation of the NLRP3 inflammasome occurs. Furthermore, we have shown that Rab11-FIP2 regulates ASC-speck formation and subsequent Caspase-1 mediated cleavage of pro-IL-1β and Gasdermin D, all hallmarks of pyroptotic cell death.

A possible explanation for this is that Rab11-FIP2 binds directly to both NLRP3 and Caspase-1, to control NLRP3 docking at trans-Golgi compartments. Furthermore, we have found that TRAM and FIP2 has opposite roles in the regulation of NLRP3 inflammasome activation, in contrast to what is the case for phagocytosis, where they collaborate (Skjesol et al. PLOS pathogens, 2019).

Furthermore, we have studied how uropathogenic *E. coli* (UPEC) mediates pyroptotic cell death in macrophage killing. We are focusing on how Rab11-FIP2 and bacterial encoded virulence factors control processes, and our results suggest that Rab11-FIP2 silencing also dampens UPEC caused pyroptotic cell death. Also, we have investigated several clinical UPEC strains and found one strain driving a particularly high level of cell death. Genome sequencing has identified that this strain encodes an arsenal of bacterial virulence factors modulating the activation of the NLRP3 inflammasome.

Our previously published data strongly suggest that the SLAMF1 receptor, which is an Ig-like receptor and a co-stimulatory molecule, has a critical role in controlling signalling from the TLR4 complexes (Yurchenko et al., *J. Cell Biol*, 2018). In 2021, we have worked on the design and optimization of SLAMF1-derived anti-inflammatory peptides that can be developed as novel drugs targeting acute inflammatory state induced by bacterial infections (sepsis).

In 2022 we have established the important role of TIRAP adaptor protein in TLR8-mediated signaling regulation, while addressing the mechanism of regulation of IFNβ secretion downstream TLR8 receptor in human monocytes.



TIRAP adaptor protein is recruited to TLR8 Myddosome, which is required for TLR8-mediated Akt kinase phosphorylation/activation. Akt kinase positively regulates IRF5 translocation to the nucleus and the expression of IRF5-dependent genes IFNbeta and IL-12A (from Nilsen et al, Biomedicines, 2022).

We found that TIRAP is recruited to the TLR8 Myddosome signaling complex (MyD88 complex with IRAK4 and IRAK1), where TIRAP positively regulates Akt-kinase activation and the nuclear translocation of interferon regulatory factor 5 (IRF5). The recruitment of TIRAP to the TLR8 signaling complex contributes to the expression and secretion of the IRF5-dependent cytokines IFNβ and IL-12p70 (Nilsen et al., Biomedicine, 2022).

Excessive inflammation mediated by bacterial endotoxin LPS may lead to death of sepsis patients due to the uncontrolled cytokines storm initiated by the innate immune cells. There are not much treatment options available for prevention. We have discovered a SLAMF1-derived peptide P7 that was able to block LPS-mediated cytokines secretion and expression *in vitro* (manuscript in preparation). The ability of P7 peptide to block TLR4-mediated signaling in vivo was tested in LPS/endotoxin shock model in collaboration with Prof. Egil Lien, UMass, USA. Our results show that mice receiving P7 before LPS injection had significantly improved survival rate (90 %) compared to mice receiving LPS alone (20 %) or control peptide followed by LPS (10 %). These findings were corroborated by measurements of body temperature, showing that pre-treatment with P7-Pen significantly reduced the drop of body temperature mediated by LPS injection. Altogether, these results demonstrated that P7-Pen could efficiently block TLR4-mediated inflammatory responses in vivo.

Major achievements 2022

- Uncovered that SLAMF1-derived peptides target both the Triffosome and Myddosome.
- Established that TIRAP adaptor is recruited to TLR8 signaling complex and required for the TLR8-mediated secretion of IRF5-dependent cytokines IFNβ and IL-12p70. (Nilsen et al, *Biomedicine*, 2022.
- Demonstrated that SLAMF1-derived peptide P7 prevents animal death in murine LPS shock model (collaboration with Prof. Egil Lien, UMass, USA).
- Established a method for making gene knock outs in virulent uropathogenic *E. coli* (UPEC) strains using CRISPR/Cas9 technology and made single gene knock mutant of Hemolysine A (*hlyA*), the cytotoxic necrosis factor 1 (*cnf1*), Omptin outer membrane protease T (*ompT*), Toll/interleukin-1 receptor domain-containing protein C (*tcpC*), that are all verified by genome sequencing.
- Established an immune functional assay that includes TLR4- and TLR8-inhibitors, various PRR-agonists, T-cell stimulants, and the immune checkpoint inhibitor anti-PD1.
  Shown that anti-PD1 has variable effects on cytokine induction in whole blood from healthy individuals, which suggest the method might be useful for identifying patients that respond favorably to immunotherapy.
- Shown that selective inhibitors of TLR4- and TLR8- can reduce cytokine production if they are added to a whole blood model even hours after viable bacteria. These reagents might therefore reveal if the TLRs drive excessive inflammation in peripheral blood in sepsis.
- Initiated a biobank with blood samples from patients with community-acquired pneumonia (CAP) and healthy controls for immunomonitoring.
- Investigated how bacterial virulence factors such as Hemolysin A and the cytotoxic necrosis factor 1 (CNF1) affect NLRP3 inflammasome activation to cause pyroptotic cell death.

Ambitions for 2023

- Finalize the manuscript "The Rab11-family interacting protein 2 is a regulator of the NLRP3 inflammasome" for publication. Here we have addressed the importance of Rab11-FIP2 in key events leading up to NLRP3 inflammasome assembly, activation and subsequent pyroptotic cell death.
- Investigate how bacterial virulence factors and Rab11-FIP2 affect NLRP3 inflammasome activation and pyroptotic cell death in human macrophages.
- Establish an immune functional blood assay for immunomonitoring of patients, including a flow-cytometry assay for immunophenotyping of leukocytes in whole blood.
- Initiate a clinical study with patients at the intensive care unit and establish a project-specific biobank with treated and non-treated patient blood samples.
- Test SLAMF1-derived peptides in an animal sepsis model.
- Complete the CAP biobank and characterize the patients' immune status using the immune functional whole blood assay.
- Initiate transcriptomic- and CyTOF- analyses of the biobank material.
- Initiate a biobank and immunomonitoring study of patients with sepsis at the intensive care unit.

Theme 2:
Molecular Mechanisms of Infection and Inflammation

Theme Manager: Professor Trude Helen Flo

Despite extensive global efforts, infectious diseases still cause significant morbidity and mortality. Further, the rise in antimicrobial resistance demands the development of novel antibiotics, for which new discoveries in 'modes of infection' and 'immune evasion' are a prerequisite. In Theme 2 we aim to decipher molecular mechanisms of infection and immune activation/evasion, test the validity of said mechanisms in animal infection models, and link them to available patient samples and data. Successful completion of the work described in Theme 2 should reveal new therapeutic targets and aid in development of host-directed therapies to be used as adjuncts to antimicrobial treatment of infections.

Main activities 2022

In theme 2 we seek to understand infection by studying both the pathogens and the host, from single cells to pre-clinical animal models and in patients. Cell death is an important host defense mechanism and is intrinsically linked with inflammation. We found that splicing factor Raver1 and pre-mRNA splicing regulates cell death, inflammation, and host resistance to bacterial infection via RIPK1/caspase-8-GSDMD signaling. We have further identified that signaling by cytokines IFN□, TNF family members, and TAK1 are also controlled by Raver1. In 2023 we will continue the work to unravel the role of Raver1 in regulating signaling and host defense against infection. We are also investigating cell death signaling pathways in neuroinflammation and microglia.

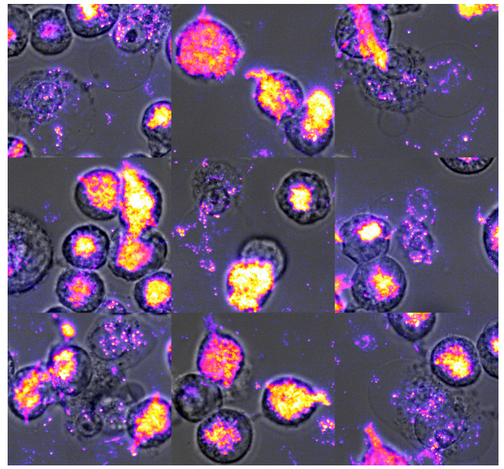
In 2021/22 prof. Flo was Fulbright visiting scholar in prof. Kagan's lab at Boston Children's Hospital/Harvard Medical School and established several new collaborations: researcher Marit Bugge came to Darrel Cottons' lab at Boston University for training on making iPSC-derived alveolar epithelial cells, and together with profs. Steinberg and Goldenberg at the Hospital for SickKids/Univ Toronto, Canada, we recently revealed that glycine's long-known cytoprotective activity is due to glycine targeting of Ninjurin1, a newly identified executioner of plasma membrane rupture. This work continues in 2023 with a focus on Ninjurin 1 cell dynamics and its role in infection-related cell death.

We have had a long-standing interest in molecular host defenses to mycobacterial infections, and virulence factors expressed by mycobacteria to evade these. We have previously identified how cytokine signaling regulates macrophage metabolism during mycobacterial infection, and this year we discovered that pyruvate import to mitochondria is a critical step in supporting RET-dependent mitochondrial ROS to Control *Mycobacterium avium* infection. We also came closer to understanding the function of some of the mycobacterial virulence factors we previously identified from screens, and we are finalizing the work showing that the common fruit fly, *Drosophila melanogaster*, can serve as a useful model organism to study mycobacterial infections and virulence factors.

Several systems-scale studies have been ongoing at CEMIR and with collaborators in Mangalore, India, and at UMass, USA. We have assembled a comprehensive multiOMICS analysis of SARS-CoV-2 infection in human lung epithelial cells and identified several putative drug targets. To our knowledge, this is the first multiOMICS study on the host response to a SARS-CoV-2 isolate from Norway. In summary, our findings show that it was a milder variant during the first wave of infections in Norway as compared to other isolates published in other international studies. This study also demonstrates that we can identify potential host-directed targets in terms of combating viral infections, and also serves as a model for any future study in the context of pandemic preparedness.

We have been establishing multicellular co-culture and organoid models to study cellular crosstalk during infection, including a lung-mimetic co-culture model of iPSC-derived macrophages and alveolar epithelial cells that will be used for studying mycobacterial- and viral infections. We have finalized an organoid method and identified how the epigenetic modulator LSD1 is critical in the defense against gut bacterial and helminth infections, by controlling epithelial effector responses. By extensively using organoid imaging, in combination with transcriptomics analysis, we were able to identify a new epithelial-intrinsic BMP-mediated pathway that limits tuft cell expansion during intestinal type 2 immune responses.

We have established an international consortium for genetic studies of severe infections and sepsis. Initially we presented data from GWAS and mendelian randomization studies on the risk of lower respiratory tract infections. We currently using various cohorts from this consortium for studies of risk of gastroenteritis and urinary tract infection.



The panel shows brightfield and total internal reflection fluorescence (TIRF) microscopy images of single immortalized mouse macrophages that have been engineered to overexpress human ninjurin 1 (NINJ1) fused to the fluorescent protein mNeonGreen. The cells have been treated with LPS and nigericin, a classic stimuli to induce the lytic cell death pathway pyroptosis. As seen in the images, the tagged NINJ1 rearranges into plasma membrane puncta as the cells blow up in response to the stimuli. This observation is in line with the protein's newly identified role as a mediator of plasma membrane lysis, in which it oligomerizes. Photo: Ragnhild S.R. Sætra.

Major achievements 2022

- Finalized and published the work describing an epithelial-intrinsic BMP signaling axis as an important mediator in tuft cell expansion during helminth infections (Lindholm & Parmar et al., *Sci Immunol*)
- Provided editorially invited commentaries on major infectious disease publications (Vornewald & Oudhoff, *Immunol Cell Biol*; Horsnell & Oudhoff, *Cell Host & Microbe*)
- Identified that glycine mediates cytoprotection by inhibiting the cell-lytic function of Ninjurin1 (Borges J*, Sætra RS* et al., *eLife*)
- Published that pyruvat supports RET-dependent mitochondrial ROS to Control M. avium infection in macrophages (Røst et al., *Front Immunol*)
- Identified identify sar5 as the gene encoding the R3 surface protein of group B Streptococci (Basson et al., *PLoS One*)
- Contributed to a study on intracellular complement component 3 in ischemia-reperfusion injury (Torp et al. *Front Immunol*)
- Published the multiOMICS-based temporal molecular network of SARS-CoV-2 infection (Pinto et al., *iScience*)
- Identified novel mechanisms of immune hijack mechanisms of SARS-CoV-2 variants including Omicron (Soorajkumar et al., *Int J Mol Sci.*)
- Identified a potential pleiotropic role of succinate receptor 1 in renal cell carcinoma tumor immune microenvironment (Najm et al., *Int J Mol Sci.*)
- Published that high levels of discordant antimicrobial therapy in hospital-acquired bloodstream infections is associated with increased mortality (Waagsbø et al, *Infect Dis*)
- Described the incidence, recurring admissions and mortality of severe bacterial infections and sepsis over a 22-year period in the population-based HUNT study (Liyanarachi et al., *PLoS One*)

Ambitions for 2023

- Complete and publish the project investigating Raver1 splicing factor and its role in innate immunity
- Complete studies on cell death signaling pathways, neuro-inflammation, and microglia
- Clarify the roles of Ninjurin1, caspase-8/1, and RIP kinases in infectious and non-infectious cell death and inflammation
- Complete and publish our work identifying a specific role for the extracellular matrix in mediating gut infections.
- Publish our work on how postnatal epithelial development drives the gut immune cell composition
- Further explore lung organoids for discoveries of the role of epithelium in immunity to infection
- Publish findings that metformin and simvastatin show pre-clinical potential as host-directed therapies to M. avium infection
- Finalize studies of TLR8 ligands as latency-reversal agents for HIV "shock-and-kill" therapy
- Complete and publish projects on mycobacterial infections of *Drosophila melanogaster* and on *M. tuberculosis* virulence genes.
- Finalize and publish collaborative work on cellular immunity of tuberculosis patients receiving adjunct treatment or therapeutic vaccine
- Publish the characterization of the iPSC-derived AT2 – macrophage co-culture model
- Elucidate the molecular mechanisms of novel differentially regulated metabolites that we identified in the metabolomics screen.
- Publish the CRISPR screens for the identification of novel host factors of HIV and Influenza A
- Identify the targets of the central kinase in innate immune signaling, TBK1, through three different proteomics-centered approaches.
- Finalize a genome-wide association study of susceptibility to upper urinary tract infections.
- Complete the studies on pharmacologic and genetic downregulation of proprotein convertase subtilisin/kexin type 9 (PCSK9) and survival from sepsis.
- Publish characterization of immune activation profiles in streptococcal necrotizing and non-necrotizing skin and soft tissue infections.
- Finish the Mendelian randomization study on circulating levels of micronutrients and risk of gastrointestinal infections, cellulitis, pneumonia and urinary tract infections.
- Publish a population-based regionwide study on prediction of Pneumocystis pneumonia in non-HIV immunosuppressed patients by combining fungal burden and comorbidity.
- Apply to the ERC Starting Grant funding scheme (M. Martín-Alonso)
- 4 PhD students will finalize their PhD work from theme 2 during 2023

Theme 3:
Molecular Mechanisms of Inflammation in Cardiovascular Disease

Theme manager: Professor Ann-Charlotte Iversen

Inflammation plays a key role in cardiovascular disease, a major cause of illness and death worldwide, with gender-specific manifestations. Formation of cholesterol crystals (CC) that mediate inflammasome activation is central to the pathogenesis of atherosclerosis. In this theme we focus on "Molecular mechanisms for cholesterol induced inflammation" and "Inflammation underlying preeclampsia and atherosclerosis", aiming to determine pattern recognition receptor (PRR)-initiated inflammation underlying preeclampsia and cardiovascular disease. To achieve this goal, we perform mechanistic molecular studies, systemic analysis of inflammatory processes and patient-oriented studies using clinical and biobank material.

Main activities 2022

In atherosclerotic plaques death of immune cells is driven by modified lipids, such as oxidised LDL. We have carried out several whole genome knockout screens to identify genes that are responsible for making immune cells more resistant or more sensitive to lipid induced death. We have discovered that modified lipids can trigger several canonical programmed death pathways and that there is a complex interplay between these death programs. We have validated the role of our top individual candidate genes discovered in our screens. Our next goal is to identify ways to modulate the function of these genes that control lipid induced cell death and test the significance of their contribution to the overall progression of atherosclerosis.

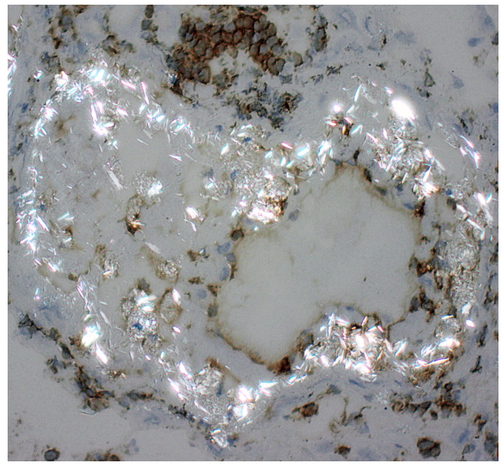
We have shown that CC is a contributing factor in thrombosis by inducing monocyte tissue factor secondary to complement. The atherosclerotic plaques contain toll-like receptor (TLR) activators and thrombosis often occur shortly following infections. Based on this, we show a potentiating effect of CC in diverse TLR-induced coagulation in human whole blood. The stimulation by CC combined with LPS, FSL-1 or CL075, serves to increase coagulation activation through monocyte tissue factor. Therapeutic intervention is investigated by relevant inhibitors (to C3, C5, CD14, NLRP3 inflammasome), and the combination of anti-CD14 with complement inhibitors (Eculizumab and CP40) are most efficient. The circulating monocytes could be important mediators of coagulation and interesting targets for treatment of thrombosis. Cholesterol accumulation, broad PRR activation, complement activation and vascular malperfusion are strongly associated to development of placental dysfunction in preeclampsia. This occurs at the maternal-fetal interaction site (in the placenta and the uterine wall decidua) and the local responses communicate with the maternal systemic response. The dynamics of how these processes interact are being revealed. Extensive maternal serum cytokine profiling has proven a sensitive measure of deviating maternal immunological development in different pregnancy disorders and is used for biomarker selection for earlier identification of pregnant women at risk. Overall, this work has added novel evidence to the involvement of PRR-mediated inflammation in development of the distinct preeclampsia subtypes and the mechanistic relation to cardiovascular disease, and led to discovery of several underlying immunological responses, maternal and fetal genetic risk factors, and novel predictive tools for hypertensive pregnancy disorders.

In 2022 we completed an exploratory sub-study of the ASSAIL-MI trial, where we examined leukocyte differential counts and their relation to myocardial salvage and peak troponin T (TnT) in STEMI patients randomised to tocilizumab or placebo. We performed RNA-sequencing on whole blood and T cells, and B and T cell subpopulations were examined by flow cytometry. We found that tocilizumab induced a rapid reduction in neutrophils and seemed to attenuate neutrophil function in STEMI patients potentially related to the beneficial effects of tocilizumab on myocardial salvage.

In a prospective study of 50 consecutive patients with out-of-hospital cardiac arrest, we examined the association between cardiac arrest characteristics and inflammatory biomarkers. Long time to return of spontaneous circulation and high lactate level at admission were associated with increased complement activation (TCC and C3bc), pro-inflammatory cytokines (IL-6, IL-8) and endothelial injury (syndecan-1) at admission. High levels of TCC and IL-6 at admission were significantly associated with increased 30-days mortality. In conclusion, inflammatory biomarkers, including complement activation, cytokines and endothelial injury, were associated with increased circulatory failure in the initial period after cardiac arrest. CC are found in all stages of atherosclerosis. How our immune system detects CC and how CC cause inflammation is not fully understood. In 2021 we published a paper in *Science Immunology* describing some of the pieces that were missed in the puzzle. Our study demonstrated that the intracellular C5 complement system is a key factor in the biological process of the sterile inflammation in atherosclerosis leading to IL-1β release from macrophages. This work has continued in 2022 with focus on importance of intracellular C5aR1 in controlling responses to cytosolic DNA and RNA.

Major achievements 2022

- Revealed that regulation of the oxidative-stress response by NRF2 in the uterine wall decidua diverged in preeclampsia with and without fetal growth restriction, reflecting a fetal protective mechanism at the maternal-fetal interface (Mundal *et al, International Journal of Molecular Sciences*)
- Defined deviant maternal immunological development throughout pregnancy in women with polycystic ovary syndrome (Stokkeland *et al, Journal of Clinical Endocrinology & Metabolism*)
- Characterized circulating levels of anti-C1q and anti-Factor H auto-antibodies and their targets in normal pregnancy and preeclampsia (Dijkstra *et al, Frontiers in Immunology*)
- Revealed that IL-6 inhibition with tocilizumab induced a rapid reduction in neutrophils and seemed to attenuate neutrophil function in STEMI patients potentially related to the beneficial effects of tocilizumab on myocardial salvage (Huse *et al, EBioMedicine*)
- Demonstrated an association between inflammatory biomarkers (such as complement and cytokines) and increased circulatory failure in the initial period after cardiac arrest (Langeland *et al, Resuscitation*)
- Detailing complex protein interaction patterns with alginate hydrogel surfaces intended for use in transplantation/cell therapy. Demonstrated that the low-inflammatory and fibrotic potentials of sulfated alginates could be due to enrichment of inhibitors from complement and coagulation (Coron *et al, Materials Today Bio*).
- Demonstrated that sulfated alginates contribute to omitting fibrosis in a transplantation model using cGMP hepatocytes (Syanda *et al, Bioengineering and Biotechnology*)



Cholesterol crystals in uterine wall decidual tissue from a preeclamptic pregnancy taken by polarized light microscopy. Photo: Bjørg Steinkjer.

Ambitions for 2023

- Identify intracellular trafficking mechanisms of C5a and C5aR1 that control mitochondrial ROS production and inflammasome activation
- Localize intracellular C3/C5 convertase in macrophages
- Establish the importance of mitochondrial C5aR1 in controlling responses to cytosolic DNA and RNA
- Determine the effects of CC and TLRs in monocyte-induced coagulation and assess effective inhibitory strategies
- Explore the systemic effects of a low-calorie restricted diet on leukocyte PRRs, thromoboinflammation, and serum cytokines
- Determine connections between serum cytokines profiles and weight-loss
- Determine the tissue localization and cellular involvement for cholesterol crystal accumulation at the maternal-fetal interface
- Combine and correlate data sets for pathological processes at the maternal-fetal interface in preeclampsia, such as cholesterol-driven inflammation, vascular malperfusion and oxidative stress
- Establish causal classification of subgroups of preeclampsia and fetal growth restriction by profiling metabolites, lipoproteins and immune mediators
- Complete extensive profiling of the maternal immune development throughout pregnancy by measuring serum cytokines in many different pregnancy complications
- Identify molecular responses characteristic for pregnancies at high risk for preeclampsia and determine how these are affected by prophylactic aspirin
- Expand collection of patient-based biobanks for translational inflammation studies
- Explore how a broad cytokine network is affected by tocilizumab in patients with STEMI (an ASSAIL-substudy)
- Examine different inflammatory biomarkers and their role in predicting outcome after cardiac arrest
- Establish a biobank for studies of septic and cardiac shock at the Intensive Care Unit at St. Olavs Hospital

Theme 4:
Molecular Mechanisms of Inflammatory Bowel Disease and Intestinal Regeneration

Theme Manager: Professor Arne Sandvik

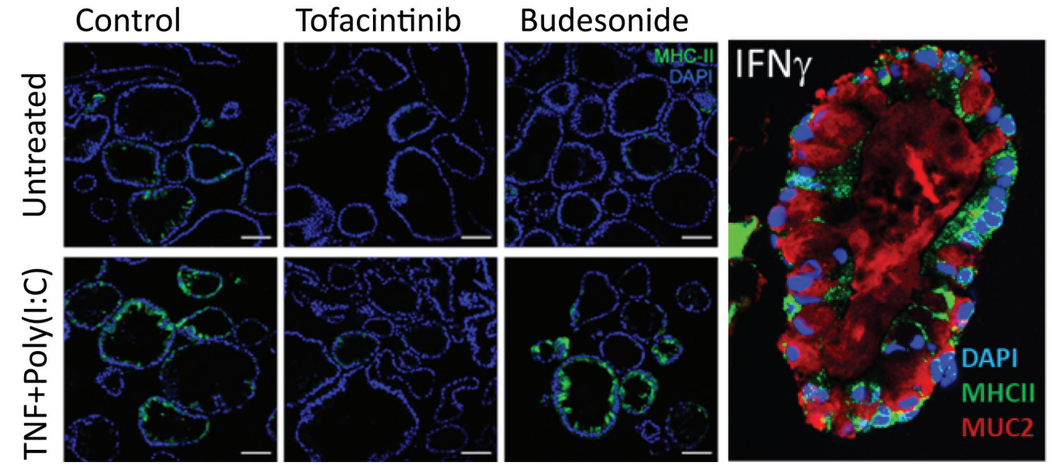
Inflammatory bowel disease (IBD) are chronic diseases arising most likely from an inappropriate inflammatory response to commensal gut microbes. It is a relative lack of in-depth studies of disease mechanisms in human-derived experimental models. This theme studies the IBD inflammatory process and its consequences at a mechanistic level with hypotheses generated from clinical material. Furthermore, we attempt to define the molecular mechanisms in intestinal epithelial reparative processes within the context of IBD and infectious diseases.

Main activities in 2022

The research group has continued studying colonic epithelial responses to immunological and physiological signals such as cytokines and chemokines. During 2022 work has encompassed the effect of IBD-approved drugs, including recently introduced JAK inhibitors, on inflammation-conditioned human organoids to prepare for coming use as real-life patient-specific bioassays to circumvent the clinical problem of heterogenous response to disease-modifying drugs. The model has been optimized by introducing a physiological low-oxygen environment rather than routine incubator conditions. Moreover, efforts have been done to modify colonoids by siRNA and CRISPR-Cas9 techniques. Long-term studies on the relation between gene expression and genomic variation through EQTL analyses have identified candidate genes linking genetics to the inflammatory process and ongoing work aims at a mechanistic understanding of these finds. As part of this, longitudinal studies in IBD patients are being wrapped up to allow correlation of clinical parameters and drug responses with colonoid behavior at the level of the individual patient. This is facilitated by established techniques for generating organoids from biopsies taken from the most informative patients and frozen for retrospective use. Other aspects of IBD pathobiology are studied together with collaborators to understand the role of adherent microbes (Yale collaboration) and innate $\gamma\delta$ lymphocytes (Singapore collaboration).

Major achievements in 2022

- The CAG-IBD project to generate highly refined patient data and material from both adults and children is well under way at four different sites, and the grant was prolonged another three years..
- A prospective intervention study aimed at predicting treatment response/loss of response, including the role of NGAL as a biomarker has been wrapped up before analyses.
- Culture conditions for colonoids have been optimized for IBD research, routinely using a 2 % oxygen concentration, and drug testing is done applying these parameters. Our results suggest that colonoids studies can and should be performed in physioxia when the resemblance to in vivo conditions is important.
- The roles of JAK/STAT signaling in intestinal epithelial cells (IECs) from colonoids, from UC patients or non-IBD controls have been explored, and we have shown how it regulates TNF+Poly(I:C)-dependent upregulation of MHC-II expression. Thus, illustrating how JAK/STAT signaling in non-immune cells could impact the adaptive immune response via antigen presentation.
- By self-developed deep learning-based image analysis we have revealed significant differences in the number and distribution of T lymphocytes, and the subset of $\gamma\delta$ T lymphocytes, in the colonic mucosa between patients with UC, CD and healthy controls, particularly in the immunologically important epithelial microenvironment.
- Studies on collagenous colitis have identified hallmarks of non-destructive IBD, and further confirmed the utility of NGAL as a biomarker for the disease.
- Studies on the clinically important process of fibrosis in Crohn's disease highlight the role of 5-hydroxytryptamine.
- A study about the interplay between the intestinal epithelium/ the microbiota and the immune cellular repertoire has been submitted for publication



Major Histocompatibility Complex (MHC)-I and -II genes are upregulated in intestinal epithelial cells (IECs) during IBD. In 2022 we published a work in *Frontiers in Immunology* showing that the pan-JAK inhibitor Tofacitinib downregulates TNF and Poly(I:C)-dependent MHC-II expression in the colonic epithelium. The images show effects of ligand and drug treatment on MHC-II protein expression in colonoids detected by immunofluorescence staining. Nuclei are stained blue (DAPI), green colour shows MHC-II protein expression. Right image shows MHCII expression in IFNg treated colonoids. MUC2 (Goblet cell marker) is shown in red. Photo: Shreya Gopalakrishnan and Marianne Doré Hansen.

Ambitions for 2023

- Manage the ongoing prospective patient studies to ensure maximally informative data and material.
- Use patient-specific colonoids from informative patients studied long-term, in prediction of drug responses.
- Further refine the colonoid model by establishing permanent genetically modified cultures for mechanistic studies.
- Delineate IBD-relevant mechanisms for intestinal fibrosis, through long-term experiments administering 5-hydroxytryptamine to rats.
- Study the interplay between the microbiota / intestinal epithelium/ immune cell in early life development
- Finalize a study on the role of smooth muscle derived factors in intestinal epithelial repair
- Study the interplay between the intestinal epithelium and the smooth muscle, in different scenarios.

Theme 5:
Molecular Mechanisms of Inflammation in Cancer Progression and Bone Loss

Theme Manager: Professor Therese Standal

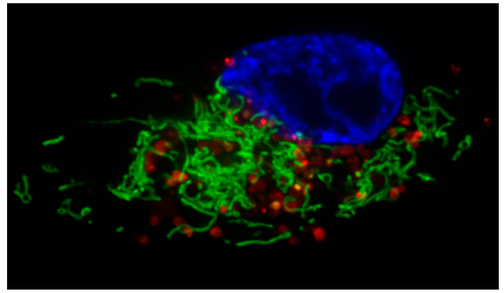
Cancer cells modulate the tumor microenvironment by secreting factors that promote chronic inflammation, inhibit immune surveillance and disrupt bone homeostasis. Pattern-recognition receptors (PRR)s are signalling immune-receptors that mediate inflammatory responses. These receptors sense pathogen or danger-associated patterns associated with stress and injury. PRRs are highly expressed on immune cells, and are promising targets in cancer immunotherapy, due to anti-tumorigenic responses they mediate in the tumor microenvironment. However, these receptors can also relay inflammatory responses in the tumor microenvironment that drive cancer progression and bone loss. Autophagy is a fundamental cell protective process where foreign, damaged, or surplus intracellular constituents are transported to and degraded in the lysosomes. As a result of this degradation of intracellular macromolecules, building blocks are released for reuse by the cell. It is well established that autophagy is induced by cell intrinsic mechanisms such as low energy (ATP) levels and lack of amino acids. Autophagy may support tumor progression by intrinsic cell mechanisms, and by cross-talks between tumor cells, tissue infiltrating immune cells and stroma. **The aim of this theme is to understand interactions between tumor cells and the microenvironment at a molecular level.**

Main activities in 2022

We have optimized in vitro model systems for studying neutrophils and plasmacytoid dendritic cells (pDC)s. Both these cell types can greatly influence T cell responses in the tumor microenvironment (TM). However, they are understudied since they are difficult to work with due to activation and assay requirements. Tumor- associated neutrophils display a high degree of plasticity and assume polarized states that are poorly understood. We have characterized human neutrophil polarization states, and found that PRR-activation in colon cancer cells can induce changes in neutrophils which could potentially impact T cell responses. We now aim to characterize neutrophils in multiple myeloma using our established methods, to determine how myeloma cells shape neutrophil polarization and how this impacts MM cell survival.

pDCs produce important Type I interferons (IFN)s that promote anti-cancer immunity, but these cells are often dysfunctional in cancers. The PRRs Toll-like receptor (TLR) 7 and 9 in pDCs induce strong IFN responses when activated by nucleic acids. We have studied IFN-signaling in pDCs and have identified a Rab GTPase that impairs TLR9 signaling which has not been described before. Further investigation is needed to understand how Rab GTPases affect TLR9 signaling in pDCs. This Rab GTPase was also found to be expressed in MM cells that express TLR9. The mechanisms of how Rab GTPase affects TLR9 signaling is being investigated further in myeloma cells since TLR9 activation in these cells can promote cell survival.

By comparing closely related benign and metastatic breast tumors, we have identified cancer cell-derived chemokines that establish and maintain an immune suppressive landscape in the metastatic tumors and unraveled a novel mechanism for how such immune cells stimulate autophagy in the cancer cells inside aggressive solid tumors. Importantly, we find that this rise in autophagy strongly reduced the levels of pro-inflammatory signaling compounds secreted from the cancer cells. We further find this cellular interplay to be initiated by cancer cells with constitutive NRF2-mediated oxidative stress signaling. Together, the findings are consistent with a model where discrete genetic changes in the cancer cells dictate infiltration of specific innate immune cells that stimulate autophagy in the cancer cells and reduce the local level of pro-inflammatory compounds in solid tumors. Moreover, the expansion of these specific immune cells is also associated with systemic effects in cancer cachexia. We are exploring the ability of these immune cells to accelerate autophagy in muscle tissue and contribute to cachectic muscle loss. In an international collaboration, we are exploring novel chemical inhibitors selective for immune cells (CSF1R inhibitor for macrophage subtypes). With these efforts, we will contribute to novel biological and chemical means to redirect immune reactions in solid tumors for future therapeutic improvements.



Mitophagy assessment via super resolution imaging in breast cancer cell line. MDAMB231 cells expressing the mitochondrial localization sequence (MLS)-EGFP-mCherry were imaged using Nikon spinning disk SoRA. Nuclues (Blue), mitochondria (green) and red (mCherry) dots representing autophagosomes in the mitochondria indicating mitophagy. The image was denoised in NIS elements software. Scale bar 2µM. Photo: Apsana Lamsal.

We have studied interactions between adipocytes and malignant plasma cells in vitro. We have also studied how diet-induced obesity influence disease progression and immune cell composition in the bone marrow in a pre-clinical multiple myeloma model. We are further studying intracellular metabolism in the cancer cells, and how manipulation of metabolic pathways can alter cell maturity and drug response.

We have designed and validated a panel of 40 antibodies that are used to stain bone marrow biopsies from myeloma patients with and without bone disease using imaging mass cytometry. We have studied which survival pathways are induced in response to TLR-signaling in multiple myeloma cells and how TLR signaling influence drug response. We have successfully knocked down IL-32 in primary T cells and studied how this influence T cell function in vitro. We have finalized our work on TLRs and IL-32 expression in multiple myeloma and the paper is now accepted for publication. We have studied how IL-32 is induced in multiple myeloma cells and are preparing a manuscript on how IL-32 protein turnover is regulated. We have further continued our work on how immunoglobulins may promote disease progression in multiple myeloma.

Major achievements in 2022

- Identified new potential markers of distinct neutrophil polarization states.
- Characterized how PRR activation in colon cancer cells induces changes in neutrophils that may influence T cell response.
- Identified a Rab GTPase that impairs TLR9 signaling.
- Identified the expression of this RabGTPase in pDCs and MM cells which express TLR9.
- Published a paper on how oxidative stress signaling relates to aggressive development of breast cancer (Wolowczyk C. et al. *Free Radic Biol Med.*).
- Performed MS-based proteomic analysis of solid tumors and correlated the findings with previously performed RNA Seq data to identify immune suppressive mechanisms associated with metastatic cancer development.
- Established autophagy- and mitophagy- reporter cell lines and used these to study cancer metabolism.
- Performed preclinical testing of novel CSF1R inhibitors in mice breast cancer models.
- Published a paper on how to automatically quantify human osteoclasts using object detection (Kohtala et al. *Front Cell Dev Biol.*)
- Published a paper on the effect of TAK1-inhibitors in the Vk*Myc multiple myeloma mouse model (Håland et al. *BMC Res Notes.*)
- Published a paper on miRNA-mRNA interactions in multiple myeloma (Aass et al. *Sci Rep.*)
- Identified mir-105-5p as a predictor for prognosis in multiple myeloma (Aass et al. *Br J Cancer.*)
- Established methods for in vitro differentiation of adipocytes from human bone marrow-derived mesenchymal stromal cells and how to co-culture them with myeloma cells and immune cells.
- Performed imaging mass cytometry on bone marrow biopsies from myeloma patients with/without bone disease

Ambitions for 2023

- Publish findings describing characteristics of neutrophil polarization states and how PRR activation in colon cancer cells induces changes in neutrophils
- Investigate how polarized neutrophils affect T cell activation.
- Characterize how neutrophils are affected by MM cells
- Describe new mechanisms of how Rab GTPases affect TLR9-mediated IFN signaling in pDCs
- Determine how Rab GTPases affect TLR9-signaling in MM cells and how this affects the survival of MM cells.
- Publish drivers for different immune cell infiltration of solid tumors.
- Publish how autophagy can be stimulated by certain immune cells and how this may influence cancer aggressiveness.
- Further unravel how NRF2 may orchestrate tumor immunity.
- Further unravel how immune cells may drive systemic cancer-related muscle loss.
- Publish our data on the effect of obesity on multiple myeloma disease progression and immune cell composition.
- Publish our data on the role of IL-32 in T cells.
- Finalize our work on the effect of TLR activation for drug sensitivity in multiple myeloma.
- Finalize our work on how manipulation of intracellular metabolic pathways influences cell maturity and drug response in multiple myeloma.

Cemir Research Groups

The Inflammation Research Group

The strategy of the Inflammation Research Group is to study the cellular and molecular mechanisms that inflammasomes, Toll-like receptors (TLRs) and the complement system are using to mount sterile and non-sterile inflammatory responses. The group has a long track record and has made several significant contributions within innate immunity and host defence over the last 25 years. Currently, we have a focus on mechanisms involved in trafficking of TLRs and their adaptor molecules between intracellular compartments where TLR signalling is taking place. This project aims to increase our understanding of how Gram-negative - and Gram-positive bacteria are able to induce inflammatory signalling from different cellular compartments, and identify new targets for treatment of severe inflammatory conditions. Moreover, we work on inflammatory responses that occur during the development of atherosclerosis. The aim of this project is to identify the detailed molecular mechanisms of how cholesterol crystals activate the complement system and immune cells. The goal is to design effective therapeutic agents to diagnose and treat atherosclerosis.

The Inflammation Research group has a strong interest in applying and developing molecular and cellular imaging techniques for use in the CEMIR projects. The group leader is also scientific leader for the Imaging Core Facility at NTNU (http://www.ntnu.edu/dmf/cmic). This core facility has recently acquired the most recent state of the art confocal microscope, the LSM880 Airyscan which is very suitable for fast live cell imaging. Also, we have a 3X STED super-resolution laser confocal microscope with a PicoQuant single molecule detection upgrade, and a TIRF microscope. In 2022 we will start installing a high content imaging system equipped with a spinning disk confocal module. These instruments are well-integrated in the CEMIR laboratories. The inflammation Research Group is collaborating with other CEMIR groups in completing the basic research oriented CEMIR themes (themes 1–4), as well as having cooperations with the more clinically orientated research themes on inflammatory bowel disease and atherosclerosis.

The research group is led by Professor Terje Espevik and currently consists of 15 persons. The group has close collaborations with the CEMIR adjunct professors, Mollnes, Lien, Fitzgerald, Stenmark and Latz. Moreover, the group is also actively involved in collaborative projects at national (B. Halvorsen, University of Oslo) and international levels (C. Kemper, NIH, USA, P. Garred, University of Copenhagen, G. Teti, University of Messina, Italy, and M. McCaffrey, University of Cork, UK).

The Autophagy and Oxidative Stress Defense Group

The autophagy group focuses on how this intracellular degradation route is controlled by external signalling compounds and local metabolite levels to regulate inflammation in normal tissues and solid tumours. Development and progression of solid tumours is influenced by the infiltrating immune cells. So-called immunologically cold tumours display clear signs of local immune suppression, develop more aggressively, and respond poorly to treatment. On the other side, immunologically "hot-tumours" show favourable prognosis and better responses to therapy. We, and many others, aim to find new ways to convert the local immune environment in solid tumours from "cold" to "hot". Autophagy can be highly selective degradation of intracellular proteins and organelles. Thus, autophagy has the potential to change the composition of intracellular signalling proteins in all cell types, including cancer cells. Activation of the Type I Interferon response is a sign of a "hot" tumour. We recently published that autophagy coincide with a dampening of the Type I interferon response in innate immune cells. We now study if immune reactions and interferon response within solid tumours is controlled by autophagy. For these studies, we combine data from tumours from an immunocompetent mouse model with data mining in large databases of tumour biopsy and clinical information. The aim is to explore the hypothesis that autophagy is a selective cellular mechanism involved in the regulation of tumour immunity. We search for causal mechanisms in the cellular interplay between transformed cancer cells and infiltrating immune cells to identify targets to reprogram tumour microenvironment in solid tumours. One of the approaches relates to tumour associated macrophages that depends on the macrophage specific receptor CSF1R. In a multidisciplinary collaboration, we explore novel CSF1R inhibitors as candidates for reprogramming tumour immunity.

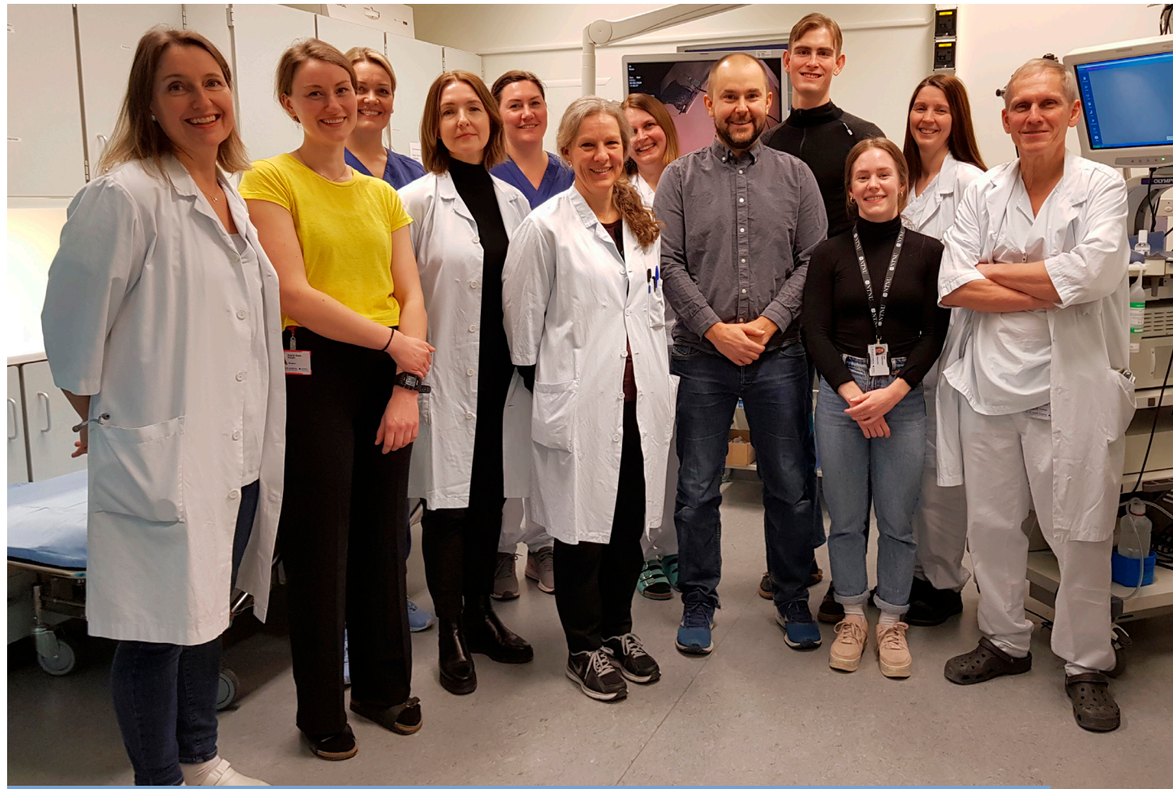
Autophagy is fundamental and strictly controlled mechanism to mobilize amino acids and other nutrients during cellular starvation. Cancer cachexia is a severe, systemic complication characterized by dramatic loss of muscle proteins. We now explore the possibility that some solid tumours secrete compounds that disturb the formation of immune cells in the bone marrow. We find that some of such reprogrammed immune cells may possess activities that stimulate local autophagy in different tissues, including muscle. The group collaborate closely with other groups at CEMIR and NTNU and with Professor Terje Johansen at the University of Tromsø and Dr. Carsten Jacobi at Novartis, Basel, on aspects of autophagy and cachexia. For novel compounds targeting macrophage activities, we collaborate with Dr. Clair Pridans at the University of Edinburgh and the Max Planck Lead Drug Discovery Center in Dortmund with manager Dr. Bert Klebl.

The Inflammation in Pregnancy Research Group (InPreg)

Pregnancy is a stress test to the cardiovascular system and the hypertensive disorder preeclampsia have shared mechanisms with cardiovascular disease. The two main causative components are placental dysfunction characterized by harmful inflammation and vascular malperfusion at the maternal-fetal interface, and dysregulated maternal inflammatory response to the placental stress. The relation to cardiovascular disease underlies our extensive molecular studies of cholesterol driven inflammation at the maternal-fetal interface, molecular characterization of atherosclerosis-like lesions in the uterine wall arteries, and identification of disease specific maternal serum cytokine patterns. The lack of diagnostic placental dysfunction markers underlies our molecular profiling and risk gene analysis by omics-technologies to characterize and identify biomarkers of placental dysfunction in preeclampsia and fetal growth restriction. The increased risk for cardiovascular disease following hypertensive pregnancy disorders is studied in Norwegian Health Registries. The Research Group is responsible for a unique collection of placental and uterine wall tissues containing atherotic lesions, an adipose tissue biobank, and preeclampsia risk gene studies in the HUNT cohort. The broad research approach involves molecular inflammation studies, biobanking, metabolomics, transcriptomics, genomics and epidemiology, made possible by strong collaboration between clinical departments and basic researchers in different disciplines.

Central collaborators include Professors Line Bjørge at Haukeland University Hospital, Eszter Vanky, Kjell Salvesen and Bård Kulseng at St. Olavs Hospital and Tone Bathen at NTNU. We work closely with other researchers at CEMIR and the core facility CMIC, particularly linked to molecular studies of lipids and cholesterol crystals, danger response activation, and serum cytokine profiling.

The Research Group is led by Professor Ann-Charlotte Iversen. In 2022, the group counted 9 persons; Professor Iversen, one senior consultant, two PhD students, three MD PhD students, one MD student and one Staff Engineer.



The Inflammatory Bowel Diseases (IBD) Group

The inflammatory bowel diseases (IBD) research group studies IBD pathobiology, with patient data and biobanks as central resources. The ultimate aim is to improve diagnostics, prognostics and treatment, and to facilitate drug discovery. Projects concentrate on epithelial dysfunction in IBD, but also include relatively specific immunological aspects such as the role of intraepithelial lymphocytes, and the mycobiome and virome of the gut. Hypotheses are generated by e.g. transcriptome analysis of biobank material from precisely characterized IBD patients; and tested in different in vitro models such as patient-derived organoids. When relevant, projects are done in close collaboration with other CEMIR groups working with e.g. innate immune mechanisms, mucosal repair and proliferation, and genome editing.

The IBD group is closely connected with clinical medicine, also through combined university/hospital positions, and collaborates with clinicians in 7 different hospitals in the Central Norway health region. The translational aspect is strengthened by being granted, and in 2022 prolonged, CAG (Clinical Academic Group) status by the Faculty of Medicine and Health Sciences in collaboration with the Central Norway Health Authority

This is a multi-site complex biobanking and longitudinal follow-up project enrolling newly diagnosed IBD patients, aiming to produce a finely-granulated set of clinical and biological data for further research on IBD in adults and children.

Work is cross-diciplinary, including cell biologists and molecular biologists in addition to clinicians and gastrointestinal pathologists. The group is closely connected with the faculty Genomics Core Facility, performing large-scale genomics studies in particular transcriptome analysis including single-cell transcriptomics. Excellent experimental animal facilities, also for genetically modified mice, are available.

Nationally, the group collaborates mainly with the Arctic University of Norway in Tromsø, and with Oslo University Hospital. A collaboration with Sintef Biotechnology and Nanomedicine has been initiated, aiming at high throughput testing of IBD drugs in patient-derived organoids. The group's international network includes Immunobiology at Yale University (New Haven, USA), Biomedical Sciences at Cedars-Sinai Hospital (Los Angeles, USA), Singapore Immunology Network, Biomedical Sciences Institutes (Singapore), and Institute of Health Research (FISABIO) (Valencia, Spain).

The Bone Microenvironment Group

Multiple myeloma is a cancer of plasma cells, located within the bone marrow. A hallmark of this cancer is the presence of a severe osteolytic bone disease, affecting nearly 80 % of the patients. The bone disease of multiple myeloma is highly aggressive, and is the cause of pain, fractures and reduced quality of life for the myeloma patients. Infections are also common, contributing to shorter life expectancy. The expected time of survival from diagnosis has increased significantly the last decade due to better treatment options, but development of drug resistance is common, and myeloma is still considered an incurable disease.

Hypoxic and ER stress and a low grade, chronic inflammation characterize the myeloma bone marrow. Our research is centered on identifying infectious and inflammatory factors present in the bone marrow microenvironment that influence plasma cell survival and cells in the tumor microenvironment. We also study how obesity influence the immune response to tumor and tumor progression. Our ambition is to understand how interactions between tumor and the microenvironment drives disease progression.

We have established a broad repertoire of protocols for differentiation of several types of cells from human primary cells. We have access to fresh, primary tumor cells from myeloma patients and our in vitro experiments are mainly performed using human primary cells. For in vivo studies we either use a traditional xenograft model allowing engraftment of myeloma cell lines, a syngeneic mouse model established in the Chesi/Bergsagel lab at the Mayo Clinic in Arizona, US, or a human-mouse scaffold model developed in the laboratory of Anton Martens, the Netherlands. This human-mouse scaffold model allows for a reconstruction of a human hematopoietic environment in scaffolds that are subsequently implanted in immune compromised mice. This model enables engraftment of primary cells from patients. The close collaboration with the clinic combined with the relevant pre-clinical models is key in our search for new treatment targets. We collaborate with Toma Tebaldi, University of Trento, on bioinformatical analyses of RNA-sequence data. We are part of the clinical academic group (CAG) for multiple myeloma research in Central Norway and we collaborate closely with the Nordic Myeloma Study Group.

The group is led by Professor Therese Standal and currently consists of one medical research student, four PhD students, one post doctor and a researcher (20 % position).

Cellular and Molecular Mechanisms in Regeneration

Reparative processes are an important part of recovery after insults. These insults can be caused by mechanical damage, inflammation, and infection. Appropriate repair is necessary to avoid development of chronic inflammatory or infectious diseases, and even cancer. We study cell-intrinsic and cell-cell communication mechanisms by which reparative and immune responses collaboratively ensure tissue protection. We use both in vivo and in vitro (organoid co-cultures) models of disease (inflammation, infection, cancer). We use CEMIR's impressive imaging infrastructure to develop automated image analysis tools for organoids and tissue sections. We combine these imaging techniques with next generation sequencing to measure changes in microbiome, gene expression, and chromatin state. We mainly study mucosal sites, as they are one of the prime interfaces between 'in' and 'out', and thus common sites for inflammation or infection. For example, we study how factors (cytokines) that are derived from immune cells induce an effector response in the intestinal epithelium. In addition, we are determining the role of different epigenetic modifiers, which alter the chromatin state of cells, in intestinal epithelial cell differentiation in general and in response to infection specifically. Finally, we are really interested in how non-immune cells, such as cells present in the smooth muscle tissue, contribute to tissue repair, immunity, and cancer by secreting so-called 'niche' factors.

We have some specific highlights worth mentioning from 2022. We published 2 peer-reviewed manuscripts and 1 preprint, all of which were comprehensive studies. In addition, we published 2 commentaries that were invited by editors. Furthermore, our group has expanded, and we have welcomed new members during 2022. Finally, Dr. Martín-Alonso was awarded a large grant from the Norwegian Cancer Society in the open call that will allow us to continue growing also in 2023.

We cannot do this work alone, and fortunately we have a range of collaborators for our different research lines that contribute with specific expertise. We are exploring immunity at other mucosal sites together with Dr. William Horsnell (University of Cape Town, South Africa). In addition, we are working with the groups of Drs. Rick Maizels (University of Glagow, UK) and Kathryn Else (University of Manchester, UK) on different intestinal helminth infection models. In addition, we work together with Dr. Pekka Katajisto (University of Helsinki, Finland) on the role of the extracellular matrix in gut repair.

This group started in 2016, is led now by Drs Mara Martín-Alonso and Menno Oudhoff and consisted in 2022 of 1 Researcher, 3 PhD students, 1 Medical Research Student, 1 MSc student, and 1 Laboratory Technician (50 %). We hope 2023 will be another fruitful year with manuscripts and new funding opportunities.

The Research Group on Molecular Mechanisms of Mycobacterial and Viral Infections (MYCOVIR)

Mycobacteria and HIV can cause life-long infections and pose a global health challenge. The COVID-19 pandemic further exemplifies how infectious diseases can paralyze society and cripple the world economy. Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), kills about 1.5 million people each year and the prevalence of non-tuberculous mycobacterial infections caused by *M. avium* is increasing in individuals who are immunocompromised. Mycobacterial infections require long treatment with antibiotics, and drug resistance is emerging. About 35 million people worldwide are infected with HIV and need life-long treatment with anti-viral drugs to survive. And despite the successful invention of vaccines for COVID-19, the pandemic has claimed close to 7 million deaths.

Our primary research focus is the molecular host defense mechanisms involved in immunity to mycobacteria, HIV, and SARS-CoV-2, and virulence strategies employed by these pathogens to parasitize host cells. Our approach to spatiotemporally dissecting host-pathogen interactions using microscopy combined with molecular techniques has led to discoveries on pathogen recognition, inflammatory signaling, and cell death. We have used different microscopy methods including time-lapse and correlative light- and 3D electron microscopy (CLEM) for determining how mycobacteria are sensed as they move within immune cells, and how they evade host defenses. Using CLEM, we were the first to image inflammasomes in situ in M. tuberculosis-infected macrophages. Our most recent work in collaboration with the Steinberg and Goldenberg labs at the Hospital for SickKids/Univ. Toronto, reveals that glycine's long-known cytoprotective activity is due to targeting of NINJ1, a newly identified executioner of plasma membrane rupture.

We have developed expertise, methods, and tools to study HIV, mycobacteria, SARS-CoV-2, and the host's innate and adaptive immune defenses both *in vitro/ex vivo* in human primary cells and cell lines and in vivo in mice. We have recently established protocols for deriving macrophages and alveolar epithelial cells from human induced pluripotent stem cells (iPSCs) and we are currently combining iPSC-derived macrophages and -epithelial cells in a lung-mimetic co-culture model to study cellular crosstalk. We have strains of Mtb, *M. avium and M. smegmatis* available with fluorescence and firefly luciferase, and we have a confocal microscope in our BSL-3 facility for live-cell imaging of Mtb, HIV and SARS-CoV2- infections. Transposon mutant libraries with more than 150 000 mutants in *M. smegmatis, M. avium*, and Mtb are available.

The group is led by prof. Trude Helen Flo and currently consists of three co-PIs/senior scientists, one researcher, 4 PhD students, two medical research students and two master students. We collaborate with research groups within CEMIR and with CEMIR affiliated professors E Lien and K Fitzgerald (Univ. Massachusetts, USA), D Underhill (Cedars Sinai) and H Stenmark (Oslo University Hospital (OUS)). Central external collaborators are JC Kagan (Boston Children's hospital, USA), B Steinberg and N Goldenberg (Hospital for SickKids/Univ Toronto, Canada), A Barczak (Ragon Institute/ MIT, Boston) P Bruheim (NTNU, Dept. Biotechnology), A Simonsen (Univ. Oslo), AM D Riise (OUS), E Rubin (Harvard, USA), N Reiling (Research Center Borstel, Germany), K Prasad (Yenepoya University, India), M Lerm (Linkøping University, Sweden).

The Systems Inflammation Research Group

Infectious diseases and inflammatory disorders are major contributors to the global burden of disease, thereby having a huge socio-economic impact. Decades of research have unraveled the arsenal of mechanisms by which the host immune system detects an invading microbe and elicit an innate immune response ensuring clearance of the pathogen while exerting a minimal damage to the host. Any failure in this chain could lead to chronic diseases such as Atherosclerosis; as well as devastating conditions like sepsis and sepsis-induced death. It is critical for the host to restore homeostasis and resolve the inflammation upon microbial infections through a collective and meticulous coordination of a number of controlled molecular events such as chromatin remodeling, transcription, translation, post-translational modifications (PTMs) and metabolic reprogramming. The systems inflammation research group aims to specifically study the role of metabolic reprogramming and PTMs (phosphorylation, acetylation and succinylation) in antiviral signaling and inflammation using state-of-the-art systems-level approaches such as mass spectrometry-based proteomics and metabolomics. Additionally, we employ CRISPR/Cas9-based genome-wide/targeted genetic screens to identify key regulators; upon viral infection such as HIV, Influenza, SARS-CoV-2, and other inflammatory stimuli. We believe that our basic research-focused systems-level approaches would yield deeper and broader understanding of inflammatory signaling which will have enormous translational potential. One of the major accomplishments in 2022 was the first multiOMICS study of the host response to SARS-CoV-2 infection using a clinical isolate from Norway and this study was published in the journal *iScience*.

We work in close collaboration with CEMIR research groups led by Terje Espevik and Trude H. Flo; as well as Per Bruheim (Department of Biotechnology, NTNU), Denis Kainov (Department of Clinical and Molecular Medicine, NTNU) and Geir Slupphaug (NTNU Proteomics Core). Our international collaborators include Kate Fitzgerald (UMASS Medical School, Worcester, USA), Kate Fitzgerald (UMASS Medical School, Worcester, USA), Egil Lien (UMASS Medical School, Worcester, USA), Giulio Superti-Furga (Center for Molecular Medicine, Vienna, Austria), Christoph Bock (Center for Molecular Medicine, Vienna, Austria), Keshava Prasad (Center for Systems Biology and Molecular Medicine, Yenepoya University, Mangalore, India), Andre Mueller (Center for Molecular Medicine, Vienna, Austria) and Akhilesh Pandey (Mayo Clinic Rochester, USA).

Innovations and Patents

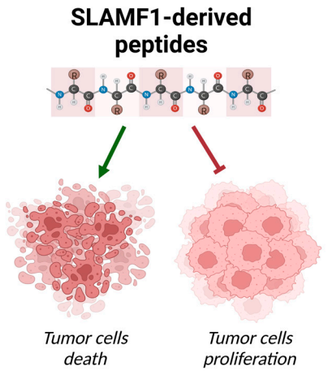
New drug candidates with a potential to kill tumor cells

Despite the extensive research in the field, cancer remains one of the major causes of death. Cancer treatment is complex and combines several approaches like surgery, radiation, chemotherapy, biological therapy, and immunotherapy. Common issues with current treatment modalities include problems such as adverse side effects and resistance, both of which severely affect the patient's quality of life. Despite the development of several advanced cancer treatment approaches in the recent years, which increased the life expectancy, many patients relapse, and many cancer types are still considered incurable. Anti-cancer peptides (ACPs), usually < 50 amino acids (AA) in length, represent a novel cancer treatment approach. Several ACPs have demonstrated the potential to inhibit tumor cells survival, and/or proliferation and/or invasiveness. The advantages of ACPs include little or no organ accumulation, high specificity and selectivity, high biocompatibility, no DNA integration and ease of modification. In CEMIR we are developing novel ACPs derived from signaling lymphocytic activation molecule family 1 (SLAMF1) with and without modifications of original SLAMF1 amino acid sequence. We have performed screens of the library of SLAMF1-derived peptides designed at CEMIR (40 peptides) for their ability to inhibit proliferation and survival of tumor cells and selected several candidates that demonstrated a remarkable cytotoxic and/or cytostatic effect against tumor cells of different origin and primary multiple myeloma (MM) tumor cells. Preliminary evaluation of peptides' mechanism of action indicate that they could induce apoptosis and inhibit pro-survival pathways in MM tumor cells. Mass spectrometry (MS) analysis revealed several potential targets relevant to these observations.

New anti-cancer peptides:

- Linked to the cell penetrating peptide (CPP) to target intracellular proteins involved in regulation of proliferation and survival of tumor cells
- Analyzed for potential targets by mass spectrometry screens with strong candidates as primary targets
- Has prominent cytotoxic and cytostatic effect towards several hematological tumor cells (myeloid leukemia (MM), other hematological cancer types)
- Are effective in concentrations that shown no toxicity towards normal PBMCs, not toxic for the healthy animals (mice, in vivo studies)

In December 2022, applications were submitted for US and EU patents based on previous PCT patent application.

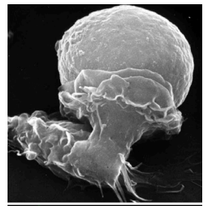


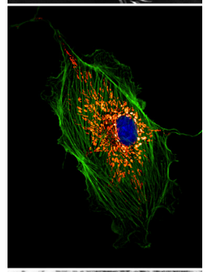
SLAMF1-derived peptides have the potential to be developed to a new anti-cancer drug.

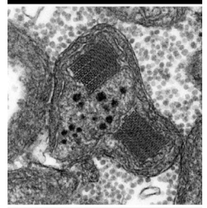
CEMIR and the cooperation with clinical departments in 2022

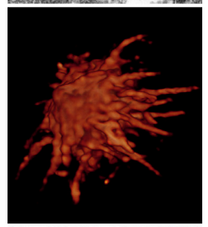
Our goal is to explore host pathogen interactions and to identify new therapeutic approaches and biomarkers for inflammatory and infectious diseases through basic research on molecular innate immune responses. Our models are relevant for different infections and inflammatory disorders such as atherosclerosis/preeclampsia, multiple myeloma and inflammatory bowel disease (IBD). We seek to exploit our findings in development of clinical and patient-oriented tools and treatment strategies. We have established a close and longstanding collaboration between CEMIR and St. Olav's hospital. Several papers from 2022 includes analyses of clinical materials including biobanks as well as epidemiological studies in large population-based cohorts. For many of our projects, we have established access to the clinical and genetic data from the large genotyped HUNT2 study linked with clinical registries such as the Mid-Norway Sepsis Registry. To illustrate the close interaction with the clinics, two groups at CEMIR are clinical academic groups (CAG). The IBD-group at CEMIR got this status in 2019.

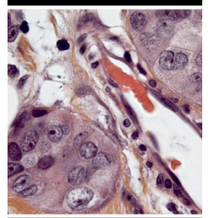
In 2020 a new CAG "Multiple Myeloma in Central Norway" was appointed. A CAG is an academic clinical research group, which consist of researchers and clinicians from the NTNU and St Olav's hospital. The two CAGs have achieved a strong professional network between CEMIR, St Olav's hospital and the rest of the health region. We have also established a strong international network of clinical groups for the studies of infectious diseases. A large international consortium exploring the genetic risk of invasive infections and sepsis is now collaboration on studies in respiratory and urinary tract infections. Moreover, in Nordic collaboration on studies on invasive streptococcal skin infections, a large database including both clinical data as well as biological samples, have been established using the local platform in HUNT cloud. Such infrastructure is of utmost importance for integrating clinical trajectories with pathophysiological mechanisms in clinical disease.

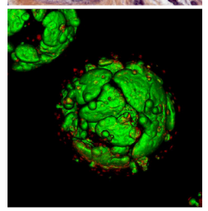












CEMIR-use of the Imaging Core Facility

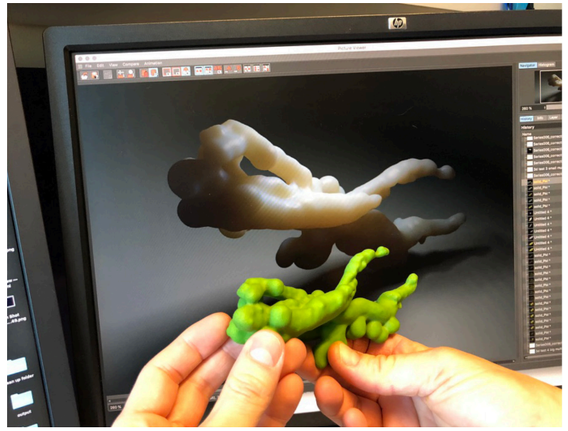
The CEMIR laboratories are located in the Knowledge Centre and the Gastro Centre at the Øya Campus of St.Olavs Hospital/NTNU. New laboratories opened in the Knowledge Centre in June 2014, and in October 2015 we opened a new Biosafety Level Three (BSL-3) laboratory, offering the highest level of security for research on viruses and bacteria in Norway.

Researchers and students at CEMIR have access to a multitude of different imaging techniques, for live cell studies as well as imaging of fixed cells and tissue preparations. These instruments are all part of the Cellular and Molecular Imaging Core Facility, CMIC, at Faculty of Medicine, NTNU, www.ntnu.edu/mh/cmic. The CEMIR director is the scientific leader for this core facility. CMIC is closely integrated with the CEMIR's laboratories and its research groups, and CEMIR scientists are the biggest user group of CMIC. The core facility offers several services: standard confocal microscopy and live cell imaging, fully automated high-throughput image acquisition, image visualization and image processing, immune histochemistry and electron microscopy.

In 2019 a Zeiss LSM 880 Airyscan super resolution confocal microscope was installed at CMIC. During the last years this microscope has become one of the most used imaging system, with the majority of users from CEMIR. This microscope uses a special 32 array GaAsP PMT detector to collect more light from the sample for each pixel, resulting in an image with better resolution and greater signal efficiency. In combination with state-of-the-art deconvolution, we can achieve resolution down to about 80 nm, which is over two times better than conventional confocal microscopes. The instrument is otherwise well equipped with an incubator system for controlled temperature and CO2 environment.

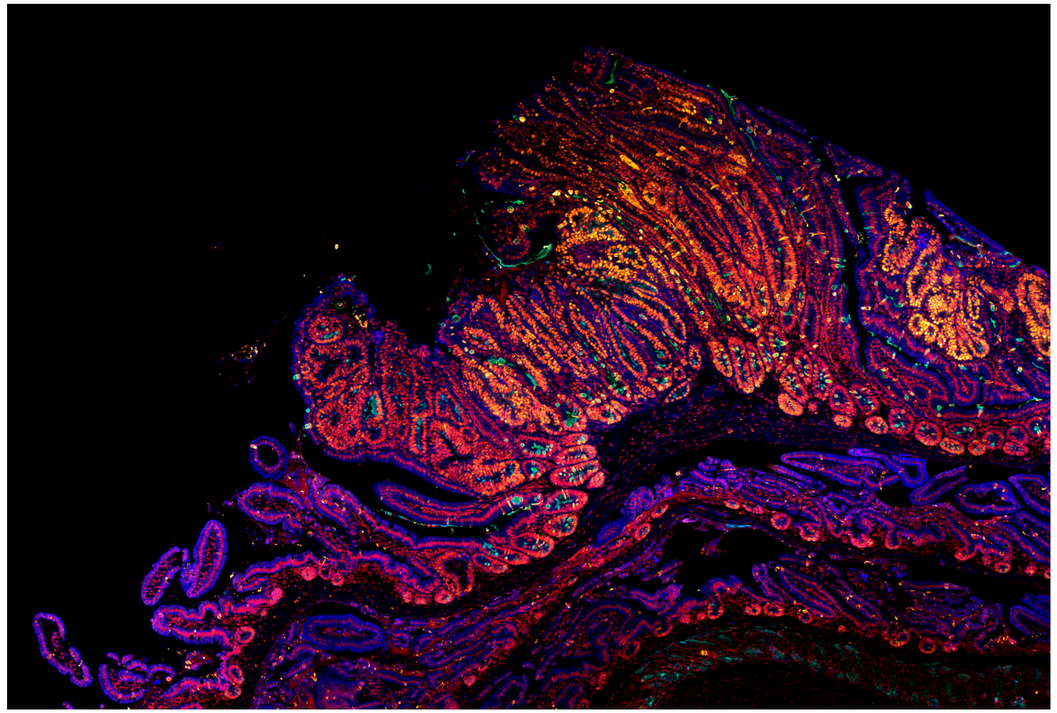
Furthermore, CMIC has a high-end Leica SP8 STED 3X super-resolution microscope with the possibility to perform single molecule detection and analysis that is particularly useful for studying molecular interactions in cells. This confocal microscope also has a Hamamatsu Orca-Flash 4.0, and in combination with new Leica Navigator software, this enables high speed fluorescence images for screening and overview. Based on high demands and a clear trend within the microscopy community we have a successful NFR application for a purpose-built high-end HCI system through the Norwegian Advanced Light Microcopy Imaging Network (NALMIN-II). In more detail this includes the newest generation high-speed confocal spinning disk or point-scan confocal, coupled with state-of-the-art large field of view sCMOS cameras, to ensure high speed image acquisition. The system will include a powerful software for quantitative image analysis through artificial intelligence and machine learning.

In addition, CEMIR researchers are using Focused-Ion Beam Scanning Electron Microscopy (FIB-SEM) in collaboration with the NTNU Nanolab. A 3-D serial block face scanning electron microscope is also a part of the CMIC instrument park, enabling larger samples at high resolution. Data is processed with Amira imaging software to give insight into the three-dimensional structures in tissue, single cells, or organelles.



Visualization of a part of a human intestine processed with iDisco tissue clearing. In this inflammatory bowel diseases (IBD) project, we 3D printed a physical model of a small piece of the structure to appreciate the intricate architecture of Ulcer Associated Cell Lineage crypts, previously possible using only serial sections.

CMIC had the opportunity to virtually experience the Zeiss Lattice Light-sheet microscope, as the first VR demo in Europe. In the coming years, we think it is likely that VR will become an increasingly important tool for showcasing and exploring the microscopic world.



"The grate wave of Duodenum Digitorum": A fluorescence microscope image of an adenoma section from the duodenum of an APCMin/+ mouse; f-actin (blue), sox9 (orange), nuclei (red), UEA-I (green). The image was taken with LSM880, 10x objective. Photo: Lilith Lee.

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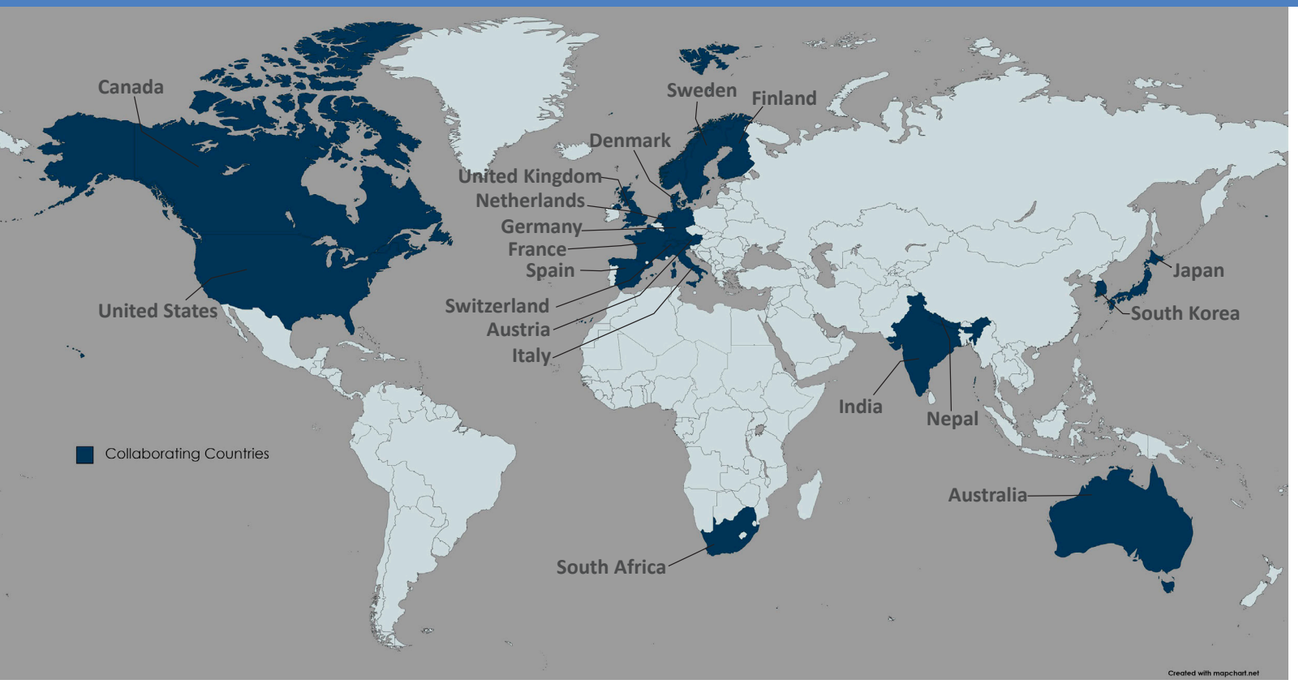
International Collaboration



It is part of CEMIR's vision to contribute to NTNU's vision Knowledge for a better world. CEMIR focuses on developing the knowledge and expertise the global community needs. International collaboration is of great importance to achieve this goal. CEMIR has a comprehensive collaboration with international scientists and institutions, and we believe that this improves the overall quality and relevance of our work. CEMIR collaborates with more than 30 international research groups. These collaborations have led to important scientific findings, joint publications and co-supervision of PhD candidates and post docs.

Six outstanding professors from other institutions are affiliated with CEMIR: Kate Fitzgerald and Egil Lien from UMass Boston, David Underhill from Cedars-Sinai LA, Eicke Latz from Univ. Bonn, and Harald Stenmark and Tom Eirik Mollnes from Oslo University Hospital.

They work in the fields of cell biology and innate immunity and contribute extensively to the research program at the Centre, as well as hosting and supervising our PhD students and post docs.

Since 2013 CEMIR staff members have stayed as guest researchers with our collaborators in USA, South Africa, England, Spain, Germany, Denmark, Singapore, Scotland and India.

English is our daily working and teaching language
34 % of the CEMIR staff is international, representing 15 different countries.

All CEMIR seminars, guest lectures and courses at master- and PhD level are held in English.

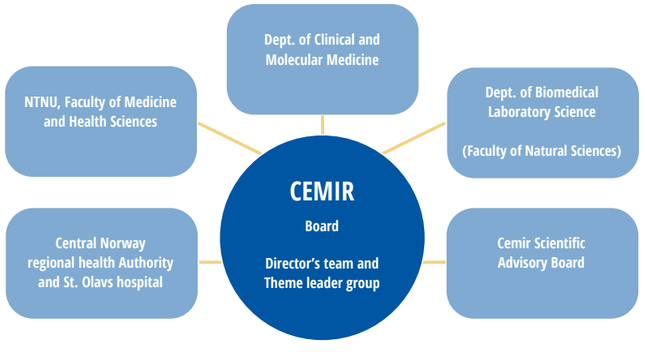
In 2021/22, CEMIR Co-Director prof. Trude Flo spent one year as Fulbright visiting scholar in prof. Jon Kagan's lab at Boston Children's Hospital/Harvard Medical School. Prof. Kagan is a world-leading scientist in innate immunity and host-pathogen interactions, where he has made several seminal discoveries. It was a rewarding year, although writing on a new CoE application and COVID restrictions somewhat limited the networking and activities outside of the Kagan lab. New collaborations were established: Marit Bugge, a researcher in the MYCOVIR group, came over to spend a week in Darrel Cottons' lab at Boston University for training on making iPSC-derived alveolar epithelial cells; a connection was made to profs. Steinberg and Goldenberg at the Hospital for SickKids/Univ Toronto, Canada and resulted in a paper co-published in eLife on a new cell-death executioner, Ninjurin 1, where people from the Kagan lab also contributed -and finally; an NIH grant was submitted together with ass. prof. Amy Barczak from the Ragon Institute/MIT/Harvard. The expanded network thus opens for new collaborations and researcher exchanges for the future.

About Cemir

The CEMIR leader group. Trude Helen Flo, Terje Espevik and Trine Aakvik Strand.

CEMIR's host department is Department of Clinical and Molecular Medicine at the Faculty of Medicine and Health Sciences, NTNU. In addition, CEMIR has two main partners: Department of Biomedical Laboratory Science at the Faculty of Natural Sciences hosting the Autophagy group, and The Central Norway Regional Health Authority/St.Olavs Hospital that has provided financing. Agreement documents regulate the co-operation with our partners. The Centre management reports to the CEMIR board.

The Centre activities integrate various research themes and unite research groups across disciplines to break new grounds in inflammation research. The Centre also has six international researchers employed as Professor II.



CEMIR board
One board meeting was held in 2022. From 2021 the board members have been:

- Magnus Steigedal – (Board chairman) Head of Dep. of Clinical and Molecular Medicine, NTNU
- Torstein Baade Rø – Vice Dean, Faculty of Medicine and Health Sciences, NTNU
- Pål Romundstad – Vice Dean, Faculty of Medicine and Health Sciences, NTNU
- Lars Gunnar Landrø – Head of Dep. of Biomedical Laboratory Science, NTNU
- Gilda Susan Opland – Head of clinic, Clinic of Laboratory Medicine, St. Olavs Hospital

CEMIR Scientific Advisory Board (SAB)
The SAB members are:

- Professor Douglas Golenbock, University of Massachusetts Medical School
- Professor Alan Aderem, Seattle Biomedical Research Institute
- Professor Göran Hansson, Karolinska Institutet
- Professor Stefanie Vogel, University of Maryland medical Center
- Professor Lynda Stuart, Vice President, Infectious Disease BioNTech

The function of SAB is to review the scientific progress of the Centre and to give guidance to future research directions.

Guest Lectures in 2022

CEMIR aims at inviting a number of guest lecturers every year. This is a great opportunity for the Centre members as well as other researchers at the Faculty of Medicine and Health Sciences to get scientific insight from excellent researchers at other universities.

Profesor Eicke Latz,
University of Bonn and affiliated professor at CEMIR.

Guest lecture: *Identification of a novel endogenous trigger of TLR4 driving metaflammation.*

Professor David Underhill,
Cedars-Sinai, Los Angeles, USA, and affiliated professor at CEMIR.

Guest lecture: *Hexokinase–VDAC–NLRP3 interactions in inflammasome assembly.*

Professor Harald Stenmark,
University of Oslo and affiliated professor at CEMIR.

Guest lectures:
Sealing holes in cellular membranes.

Professor Egil Lien,
University of Massachusetts Medical School, USA, and affiliated professor at CEMIR.

Guest lecture:
Regulation of inflammation and cell death via caspase-8.

Completed PhDs in 2022

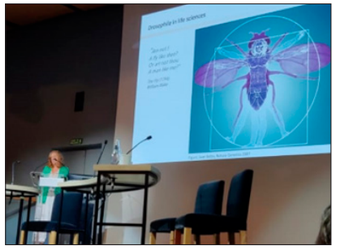
Live Marie Tobiesen Stokkeland
defended her thesis "Cytokine profiling as a measure of immunological development and deviation throughout pregnancy in healthy women and women with PCOS" June 13., 2021.

Professor Eszter Vanky, Professor Ann-Charlotte Iversen and associate professor Guro F. Giskegård have been her supervisors.

Science Communication and Outreach Activity

CEMIR members contributed with scientific presentations at many conferences and meetings worldwide in 2022, such as:

- 14th International Conference on Complement Therapeutics, Rhodes, Greece
- 3rd International Symposium on Aortic Disease, Bonn, Germany
- Gordon Research Conference on Lysosomes and Endocytosis 2022: Physiological Adaptations of the Endo-Lysosomal System
- EMBO Workshop on Tuberculosis 2022
- United European Gastroenterology Week UEGW 22
- 3rd Norwegian myeloma workshop
- Invited talk at NIH /NIAID, Bethesda, USA
- IBA Annual Meeting
- The 13th International Congress on Autoimmunity
- Drug discovery targeting inflammation, Ørebro, Sweden
- Boston TB meeting
- Norsk Biokjemisk Selskap Kontaktmøte, Tromsø, Norway
- Invited talk at University of Connecticut Molecular and Cell biology
- Invited talk at «Fedmekunnskap: Status og framtid», Tromsø, Norway
- Invited talk at University of Connecticut Health School of Medicine
- Department seminar series
- «Forelesningsserie Kunnskapsbyen Trondheim» (DKNV)
- Keystone Symposia: Innate Immunity: Complement and Beyond, Snowbird, USA



Marte Singsås Dragset gave a presentation at the conference "EMBO Workshop on Tuberculosis 2022" that was held at Institut Pasteur, September 12–16, 2022.

Ignacio Catalan Serra participated at the meeting United European Gastroenterology Week UEGW 22 in Vienna where he gave a presentation on: "Prevention and management thromboembolism as a complication of inflammatory bowel disease".

Anders Jarmund was interviewed by Diagnostics World about the work that he and CEMIR coworkers have published in Frontiers in Immunology and Journal of Clinical Endocrinology and Metabolism.

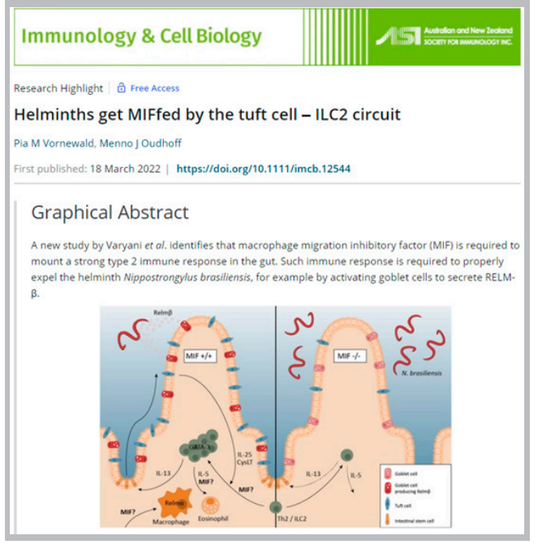
CEMIR people and our biosafety level 3 lab were involved in an NRK article about the black plague.

Etter 700 år kan en av historiens verste bakterier gjøre opp for seg.

Begge er kledd i flere lag med beskyttelsesutstyr og er omgitt av spesielle filter og luftesystemer. Vi er ikke nervøse her inne. Under Coviud var dette det tryggeste rommet vi kunne være i, sier Niruja Sivakumar.

Professor Egil Lien er ekspert på svartedaudenbakterien. Kompetansen hans brukes av både NTNU i Trondheim og utenlandske universitet.

Pia Vornewald and Menno Oudhoff were invited to write a 'news and commentary' piece in Immunology and Cell Biology.



Prizes and awards in 2022:

Professor Tom Eirik Mollnes received in 2022 the gold medal from the European Complement Network for excellent research on complement in Europa. Mollnes was also appointed as honorary doctor at Copenhagen University. Professor Harald Stenmark received the Anders Jahres medical price.

ECN Gold Medal to Tom Eirik Mollnes

Tom Eirik Mollnes was awarded the Gold Medal of the European Complement Network, which is the European Society for all Complementologists.

PRISVINNER: Professor Harald Stenmark leder Senter for kreftcelle-programmering (CanCell), et senter for fremragende forskning ved UiO. Han mottar Anders Jahres store medisinska pris for 2022. Foto: Øystein Horgmo, UiO.

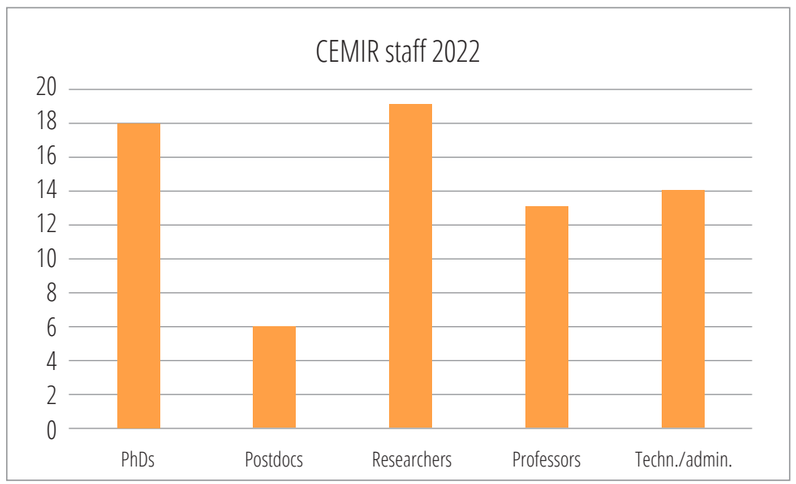
Harald Stenmark får Anders Jahres store medisinske pris

– Det er gledelig at priskomiteen verdsetter betydningen av basal celebiologisk kreftforskning, sier UiO-professor Harald Stenmark.

Cemir Staff 2022

CEMIR was established as a Centre of Excellence January 1, 2013. We have emphasized the importance of establishing a unified research Centre in which multidisciplinary research cooperation is encouraged and stimulated.

By the end of 2022, 56 scientific staff members, 13 technicians, 16 students and one administrative coordinator were associated with the Centre.



CEMIR Symposium

October 12. the annual CEMIR seminar was arranged, where CEMIR researchers and three of our affiliated professors presented their work.

Name		Research group	Nationality	Position
Aass	Kristin Roseth	Bone disease	Norway	Postdoctor
Alonso	Mara	Regeneration	Spain	Researcher
Andersen	Sonja	Support group	Norway	Staff engineer
Årseth	Charlotte	Bone disease	Norway	Sci.ass.
Bjørkøy	Geir	Autophagy	Norway	Professor
Bokil	Ansooya	Autophagy	India	Stipendiat
Boyartchuk	Victor	Inflammation	Ucraine	Researcher
Brigant	Benjamin	Inflammation	France	Postdoctor
Buene	Glenn	Bone disease	Norway	Staff engineer
Bugge	Marit	MYCOVIR	Norway	Researcher
Cemalovic	Ena	Inflammation	Bosnia and Herzegovina	PhD candidate
Damaas	Jan K	Inflammation	Norway	Professor
Diez	Alberto	Regeneration	Spain	Postdoctor
Dragset	Marte Singsås	MYCOVIR	Norway	Researcher
Egeberg	Kjartan	Inflammation	Norway	Staff engineer
Espevik	Terje	Inflammation	Norway	Professor
Fitzgerald	Kate		UK	Professor II
Flo	Trude Helen	MYCOVIR	Norway	Professor
Giambelluca	Miriam	Autophagy	Spain	Researcher
Gidon	Alexandre	MYCOVIR	France	Researcher
Granlund	Atle Van Beelen	IBD	Norway	Researcher
Haug	Markus	MYCOVIR	Germany	Researcher
Husebye	Harald	Inflammation	Norway	Researcher
Iversen	Ann-Charlotte	InPreg	Norway	Professor
Kandasamy	Richard Kumaran	Systems inflammation	India	Førsteamanuensis
Kastnes	Martin	Bone disease	Norway	PhD candidate
Kojen	June Frengen	Support group	Norway	Staff engineer
Lamsal	Apsana	Autophagy	Norway	PhD candidate
Latz	Eicke		Germany	Professor II
Lee	Lilith	Regeneration	Norway	PhD candidate
Lian	Tone Aksnes	MYCOVIR	Norway	PhD candidate
Lien	Egil		Norway	Professor II
Louet	Claire	Support group	France	Staff engineer
Ma	Qianli	Bone disease	China	Postdoctor
Marstad	Anne	MYCOVIR	Norway	Staff engineer
Mediaas	Sindre Dahl	MYCOVIR	Norway	PhD candidate
Mestvedt	Ingvild Bergdal	Inflammation	Norway	Researcher
Moen	Siv	Bone disease	Norway	Researcher
Mollnes	Tom Eirik		Norway	Professor II
Nedal	Tonje	Bone disease	Norway	PhD candidate
Nilsen	Nadra	Inflammation	Norway	Researcher
Nilsen	Kaja Elisabeth	Inflammation	Norway	PhD candidate
Niyonzima	Nathalie	Inflammation	Burundi	Researcher
Nonstad	Unni	Support group	Norway	Staff engineer
Oudhoff	Menno	Regeneration	Netherlands	Researcher
Pettersen	Kristine	Autophagy	Norway	Researcher
Pinto	Sneha Maria	Systems inflammation	India	Postdoctor
Rad	Leila Heidary	Regeneration	Iran	Staff engineer
Ragunathan	Kalaiyarasi	Inflammation	Sri Lanka	PhD candidate
Rakner	Johanne Johnsen	InPreg	Norway	PhD candidate
Rasheed	Kashif	Inflammation	Pakistan	Postdoctor
Rokstad	Anne Mari	Inflammation	Norway	Researcher
Roseth	Ingrid Aass	Bone disease	Norway	PhD candidate
Ryan	Liv	Support group	Norway	Staff engineer
Sætra	Ragnhild	MYCOVIR	Norway	PhD candidate
Sandvik	Arne	IBD	Norway	Professor
Selvik	Linn-Karina	MYCOVIR	Norway	Staff engineer
Serra	Ignacio Catalan	IBD	Spain	Postdoctor
Sivakumar	Niruja	MYCOVIR	Norway	PhD candidate
Sporsheim	Bjørnar	Support group	Norway	Staff engineer
Standal	Therese	Bone disease	Norway	Professor
Steigedal	Magnus	MYCOVIR	Norway	Researcher
Steinkjer	Bjørg	Support group	Norway	Staff engineer
Stenmark	Harald		Norway	Professor II
Stenvik	Jørgen	Inflammation	Norway	Researcher
Stokkeland	Live	InPreg	Norway	PhD candidate
Strand	Trine Aakvik	Support group	Norway	Head of administration / Staff engineer
Subbannayya	Yashwanth	Systems inflammation	India	Researcher
Sundan	Anders	Inflammation	Norway	Professor
Tryggestad	Synne	Bone disease	Norway	PhD candidate
Underhill	David		USA	Professor II
Vik	Randi	Support group	Norway	Staff engineer
Vornewald	Pia	Regeneration	Germany	PhD candidate
Wolowczyk	Camilla	Autophagy	Norway	Postdoctor
Yao	Rouan	Regeneration	USA	PhD candidate
Yurchenko	Mariia	Inflammation	Ucraine	Researcher

Cemir Scientific Publications 2022

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Comprehensive small RNA-sequencing of primary myeloma cells identifies miR-105-5p as a predictor of patient survival. *British Journal of Cancer* 2022

Aass, Kristin Roseth; Nedal, Tonje Marie Vikene; Tryggestad, Synne Stokke; Haukås, Einar; Slørdahl, Tobias Schmidt; Waage, Anders; Standal, Therese; Mjelle, Robin.
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Inflammatory Markers, Pulmonary Function, and Clinical Symptoms in Acute COVID-19 Among Non-Hospitalized Adolescents and Young Adults.
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MS-proteomics provides insight into the host responses towards alginate microspheres. *Materials Today Bio* 2022 ;Volum 17. s.1-20

Damoah, Christabel Esi; Snir, Omri; Hindberg, Kristian Dalsbø; Garred, Peter; Ludviksen, Judith K; Brækkan, Sigrid Kufaas; Morelli, Vania Maris; Mollnes, Tom Eirik; Hansen, John Bjarne; Smith, Erin N.; Brumpton, Ben Michael; Frazer, Kelly A.; Gabrielsen, Maiken Elvestad; Hveem, Kristian; Lindström, Sara; Wang, Lu; Gordon, William; Van Hylckama Vlieg, Astrid; de Andrade, Mariza; Brody, Jennifer A.; Pattee, Jack W.; Haessler, Jeffrey; Chasman, Daniel I.; Suchon, Pierre; Chen, Ming-Huei; Turman, Constance; Germain, Marine; Wiggins, Kerri L.; MacDonald, James; Armasu, Sebastian M.; Pankratz, Nathan; Jackson, Rabecca D.; Nielsen, Jonas B.; Giulianini, Franco; Puurunen, Marja K.; Ibrahim, Manal; Heckbert, Susan R.; Bammler, Theo K.; McCauley, Bryan M.; Taylor, Kent; Pankow, James S.; Reiner, Alexander P.; Deleuze, Jean-François; O'Donnell, Chris J.; Kim, Jihye; McKnight, Barbara; Kraft, Peter; Rosendaal, Frits R.; Heit, John A.; Psaty, Bruce M..
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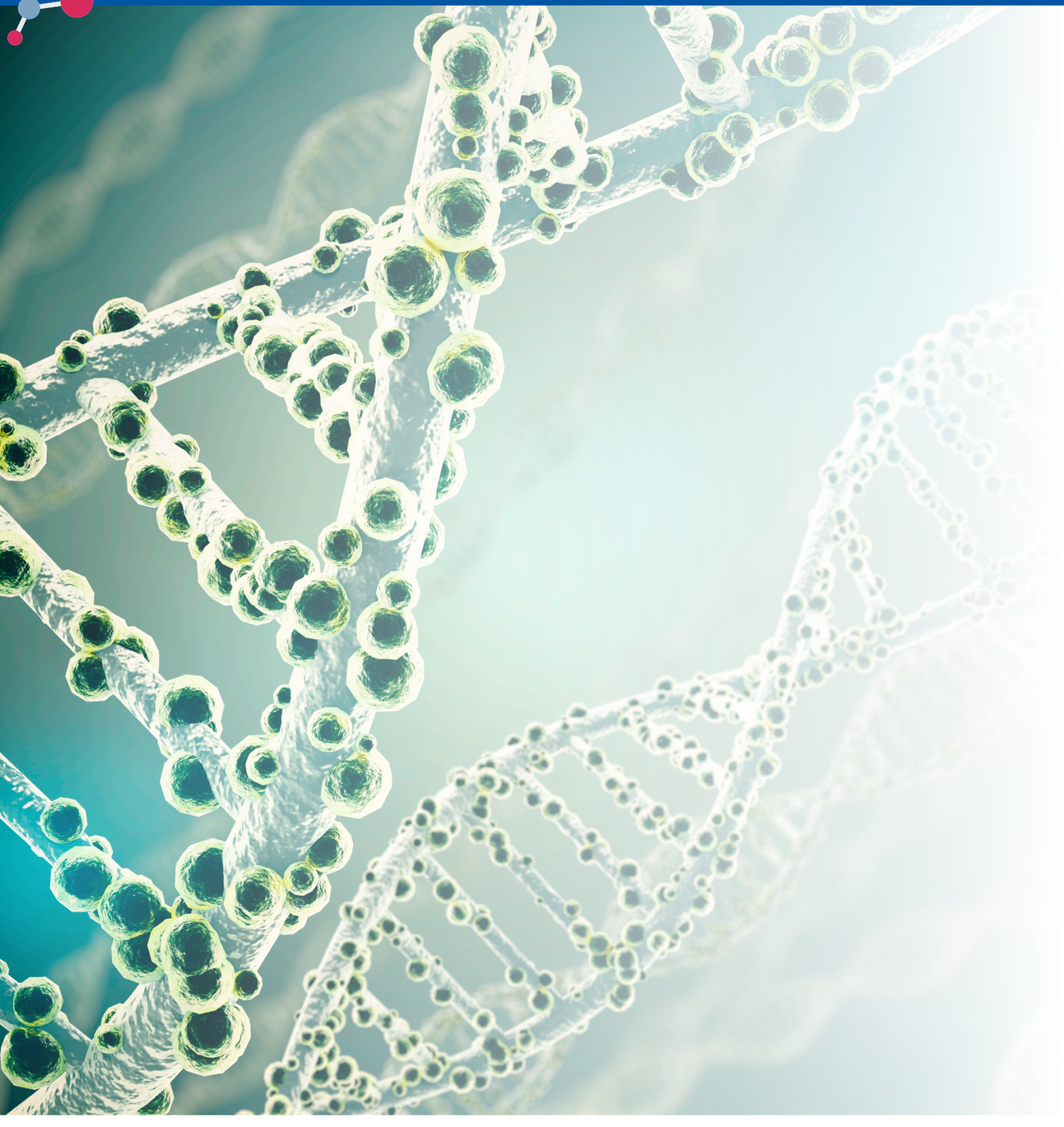

Funding and Expenditures 2022

Funding (1000 NOK)	2022
NTNU	13 141
Research Council of Norway (RCN) – Centre of Excellence grant	14 777
Other RCN funding	9 271
Other public funding	9 501
Other private funding	2 327
International funding	134
Total funding	**49 151**

Expenditures (1000 NOK)	2022
Personnel and indirect costs	37 176
Equipment	86
Other operating costs	12 722
Year result transferred to 2023	-833
Total expenditures	**49 151**

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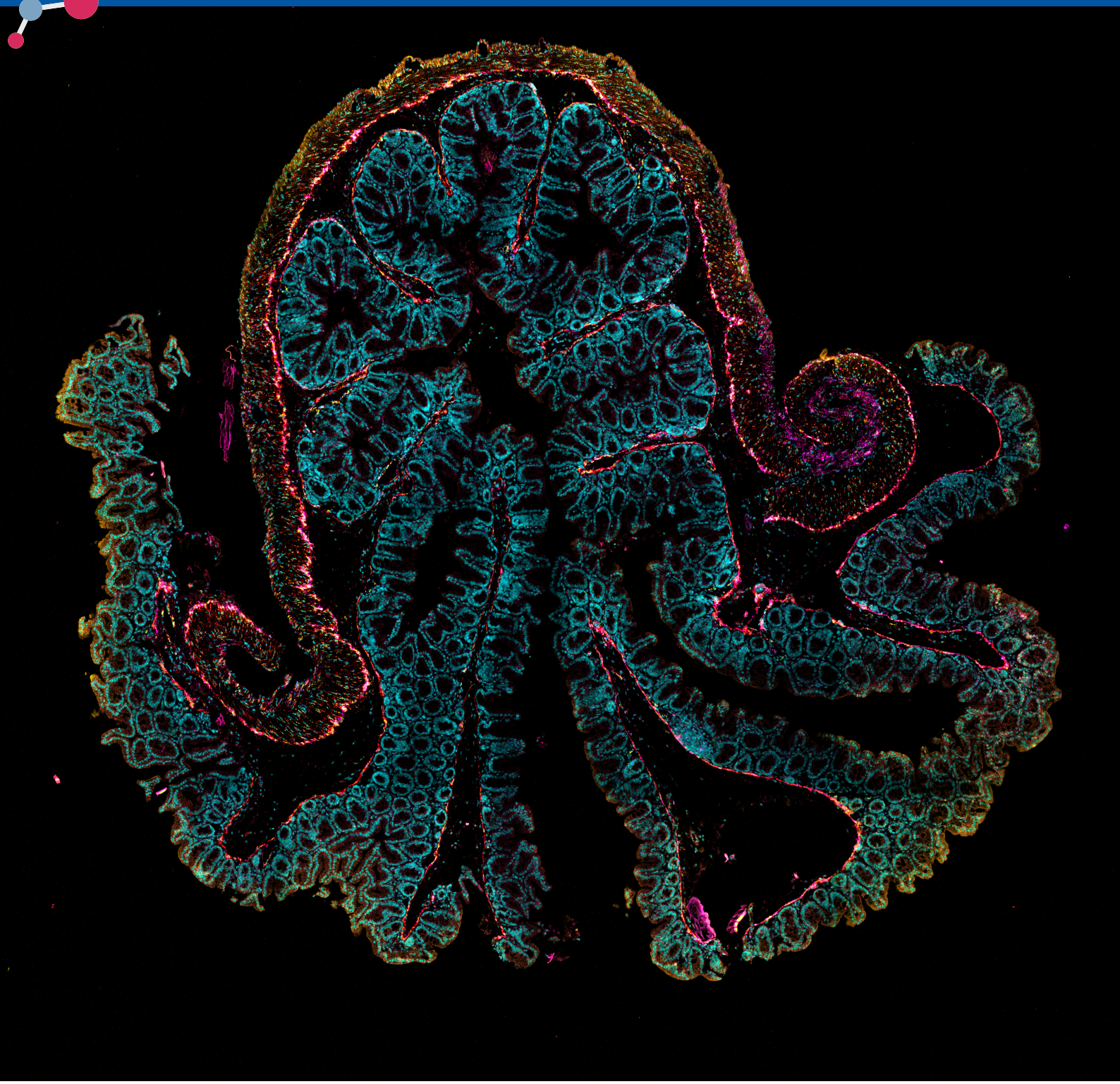
Last page:
"Octopus with Mozart wig". The picture shows a section of mouse intestinal tissue stained using FISH for 3 different BMP inhibitor mRNAs (yellow, red, magenta). Nuclei stained with Hoechst (cyan). Photo: Pia Vornewald and Lilith S. Lee.



HELSE MIDT-NORGE

ST. OLAVS HOSPITAL
TRONDHEIM UNIVERSITY HOSPITAL

NTNU
Norwegian University of
Science and Technology