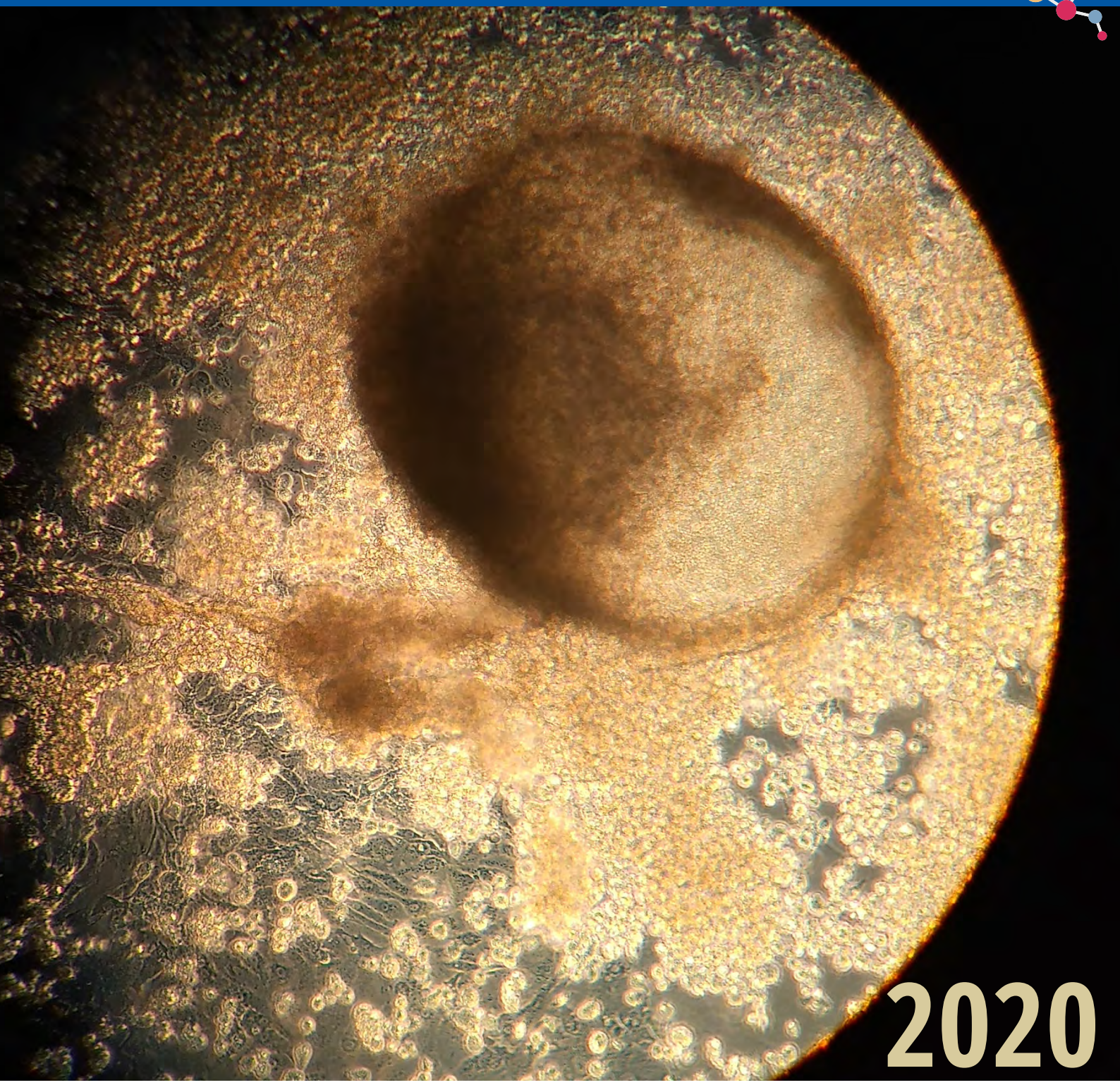


2020

Norwegian Centre of Excellence
The Research Council of Norway

CEMIR
Centre of Molecular Inflammation Research

Table of Content

Cover photo:
Title: «Planet of the EBs»
Embryoid bodies in culture, producing monocytes. Derived from human induced pluripotent stem cells.
Taken through light microscope @10x magnification with phone camera.
Photo: Håvard Styrkestad Haukaas.

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. Looking back, there has been many productive years since the establishment of CEMIR in 2013. The first years, the main priority was to establish a unified research group in which multidisciplinary collaboration was encouraged and stimulated. To improve and strengthen the scientific quality and scope of our center two new group leaders were recruited. In 2014, all CEMIR research activities were moved to the new Knowledge Centre at Øya Campus in Trondheim, which hosts first-class laboratories with state-of-the-art cellular imaging instruments. In October 2015 we opened a new 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.

In 2017 CEMIR was mid- term evaluated by an international evaluation committee appointed by the Research Council of Norway (RCN). The committee also visited the Centre in June, 2017. CEMIR received a brilliant evaluation and based on this, the Research Council decided to continue the funding for the last 5 years.

CEMIR has grown to be a vibrant and dynamic center with 67 scientific staff members, 14 engineers, 21 students and one administrative coordinator. In 2017, CEMIR formally became a research unit in the newly established Department of Clinical and Molecular medicine. This secures the process towards a continuation of the Centre when the RCN funding ends in 2022.

Every month CEMIR members meet for Journal Club. From 2018, the Journal Club has been organized by CEMIR postdocs. A small group of scientists with different areas of research present a paper and lead the following scientific discussion. The Journal Club serves several purposes: to share scientific news, to critically review and discuss the scientific findings and approaches used to reach conclusions, and to encourage collaboration between CEMIR groups. The Journal Club has been a great success as it has sparked good discussions and engagement.

The scientific activities at CEMIR have proceeded with very good progress. In 2020 57 papers have been published. CEMIR researchers have published a total of 450 articles since 2013, several in high quality journals like Nature, Nature Immunology, Nature Communications, Autophagy, PNAS, Plos Pathogens, Cell, Science, Science Advances, Blood and J Cell Biol. Several of our papers have obtained front cover illustrations in journals. 37 CEMIR PhD students have defended their theses and successfully completed their PhDs.

2020 has been a difficult year due to the Coronavirus pandemic. This situation has resulted in some delays in progress of projects. However, with proper infection control, it has been possible to keep labs open most of the time. Some of the CEMIR researchers have even started new covid-19 projects. Professor Tom Eirik Mollnes published in PNAS this year that systemic complement activation is associated with respiratory failure in covid-19 patients.

CEMIR has a strong focus on basic innate immunity and how it relates to human inflammatory diseases. The combination of basic and translational research has been incorporated into five new themes to be accomplished for the last period. Research from CEMIR has given new knowledge about mechanisms and new targets for treating inflammatory diseases like infections and cardiovascular diseases. This will help us in achieving the primary goal to identify new therapeutic targets and diagnostic tools for inflammatory diseases. Some of our research has already resulted in new drug candidates with the potential to inhibit unwanted inflammation. In order to show the impact of our research, it will be 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). 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. Despite the large amount of research, we still do not know much about the cell biological mechanisms on how TLRs and their adapter proteins control killing of bacteria. We have now 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 transports cargo along actin filaments. 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 also have a research focus on the combined effects of complement and TLRs in phagocytosis and host defence against bacteria. Moreover, we have made discoveries pointing to mechanisms on how Mycobacterium avium initiates inflammatory signalling from TLRs in the phagolysosome, however, a fraction still escapes the phagolysosome by modifying the compartment. In Theme 1, we aim to obtain more detailed mechanistic understanding of phagocytosis, phagosomal maturation and phagosomal signalling for mounting killing of bacteria.

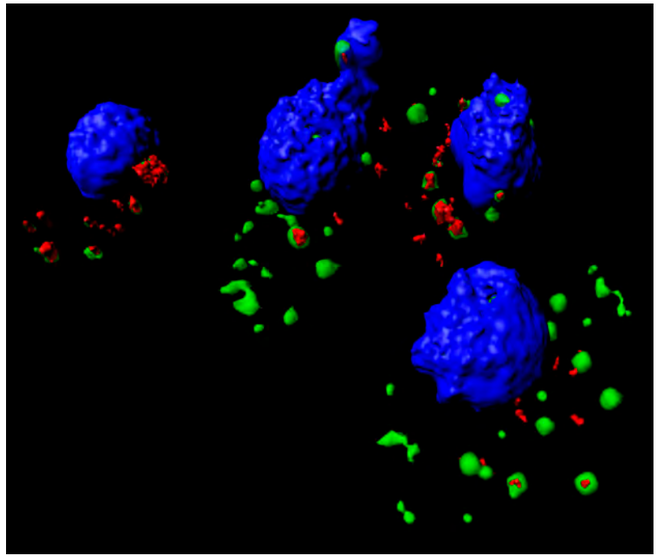
Main activities 2020

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 key role in the upregulation of pro-IL-1β and NLRP3 protein levels, and to regulate Caspase-1 mediated cleavage of pro-IL-1β that is a hallmark of pyroptotic cell death. A possible explanation for this is that Rab11-FIP2 binds directly to both NLRP3 and Caspase-1 to regulate this process. Furthermore, we have studied how uropathogenic *E. coli* (UPEC) mediates macrophage killing and induction of pyroptotic cell death. We are focusing on how Rab11-FIP2 and bacterial encoded virulence factors control processes, and preliminary results suggest that Rab11-FIP2 silencing dampens pyroptotic cell death. Also, the bacterial virulence factor, hemolysin A plays a key role in pyroptotic cell death caused by this UPEC strain.

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 2020, 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). Various modifications of the peptides were tested in different model systems – macrophages-like cell line, primary human monocytes and macrophages, and human whole blood assays.

We showed previously that human TLR8 is a main sensor of Gram-positive bacteria (Bergstrom et al., *J Immunol,* 2015). Blocking TLR8 might be a new anti-inflammatory strategy in sepsis, but this could also pose a risk by attenuating critical antibacterial effector mechanisms such as phagocytosis and intracellular killing. In 2020 we investigated this possible risk, the signalling crosstalk mechanism of TLR2 and TLR8, and the role of TLR8 and NLRP3 in monocyte death during Gram-positive infection.

We have a continuing focus on the cell biology of mycobacterial infection in macrophages and how trafficking of mycobacteria is coupled to activation of inflammatory signalling from different intracellular compartments. In 2020 we published our discovery that *M. tuberculosis* induces inflammasome activation and pyroptosis by causing plasma membrane damage in infected macrophages, which can facilitate spread (Beckwith et al., *Nat Comm* 2020). We have previously shown that *M. avium* escapes recognition by TLR8 and degradation in phagolysosomes by modulating trafficking and establishing in a unique compartment (Gidon et al., *PlosPathogens* 2017). As a follow-up to this, we show that killing with antibiotics routes *M. avium* from this unique compartment to phagolysosomes without activation of inflammation, suggesting these phagolysosomes are devoid of TLRs (Åsberg, Mediaas et al., JLB 2020).



Co-localization of Rab11-FIP2 (red) and an inflammasome component (ASC, green) in macrophages stimulated with LPS and nigericin. Blue: nuclei. 3D rendering of confocal z-stacks. Photo: Harald Husebye.

Major achievements 2020

- We have established a method for making gene knock outs in virulent uropathogenic *E. coli* strains using CRISPR/Cas9 technology.
- Constructed several SLAMF1 peptides linked to the cell penetrating peptides (CPPs) that were very effective in taking down inflammatory responses induced by TLR4.
- Uncovered several new interacting proteins for the SLAMF1 receptor that play crucial role in TLR4 signalling that could be targeted to control TLR4-mediated pro-inflammatory responses.
- Submitted a patent application for the therapeutic binding agents (application number is GB 2008888.6, filing date 11.06.2020) and started preparing manuscript for publication.
- Showed that TLR8 inhibition neither impairs phagocytosis nor intracellular killing of bacteria.
- Completed a study on how TLR8 and complement together regulate antibacterial responses in blood (Ehrnström et al., *Frontiers in Immunology*).
- Revealed a synergistic effect of TLR2- and TLR8- signalling that affected modification of IRAK1.
- Published the discovery that M. tuberculosis induces inflammasome activation and pyroptosis by causing plasma membrane damage (Beckwith et al, *Nature Communications*).
- The work on how antibiotic treatment routes *M. avium* to phagolysosomes without triggering proinflammatory cytokine production made Frontline Science with Editorial Commentary upon publication (Åsberg, Mediaas et al., *J Leukoc Biol*: Editorial commentary by Lösslein & Henneke, doi:10.1002/JLB.3CE0520-104R).

Ambitions for 2021

- Finding the mechanisms how Rab11-FIP2 controls the intracellular trafficking of inflammasome components and inflammasome assembly.
- Investigate how bacterial virulence factors cause macrophage cell death and the involvement of Rab11-FIP2 in this process.
- Defining interaction motifs in Rab11-FIP2 that bind to inflammasome components.
- Uncover the molecular mechanisms of how the SLAMF1 receptor controls pro-inflammatory signalling in human macrophages.
- Test SLAMF1-derived peptides in an animal sepsis model.
- Nail down the exact mechanism of action for the SLAMF1-derived anti-inflammatory peptides and work on their further optimization.
- Clarify the impact of IRAK1 modifications and the Mal/TIRAP adapter in the TLR8-IRF5 signalling pathway.
- Characterize the variation among isolates of *S. aureus* and GBS in the whole blood challenge model.
- Elucidation of necrotic cell death pathways induced by *M. tuberculosis* in macrophages.
- Establish the consequences of phagosomal membrane damage in *M. tuberculosis* infected macrophages.

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 2020

In theme 2 we seek to understand infection mechanisms by studying both the pathogens and the host. Several papers were published from theme 2 in high-ranking journals. One of them was our first work on HIV, showing that viral RNA is detected by TLR8 in T cells. We also found that TLR8 ligands effectively reversed latency of HIV from patients on anti-retroviral therapy. The mechanism behind and further development of these findings towards "kick-and-kill" therapeutic HIV strategies are ongoing.

In 2020 we have continued to look at the effect of pre-mRNA splicing and splicing factors on cell death and inflammation induced via RIPK1/caspase-8. We have also investigated post-translational modifications in the same pathway. In addition, we have studied regulation of Pyrin-caspase-1 inflammasome activation. OMICs approaches are now fully developed at CEMIR and we have completed proteomic characterizations of human T cells and macrophages, and post-translational modifications in viral respiratory infections.

We have identified an autocrine/paracrine cytokine signaling loop in Mycobacterium avium infected macrophages that activates a metabolic enzyme with anti-mycobacterial activity. We have also tested several drugs for host-directed therapeutic potential to M. avium infection and identified a few promising candidates. This period we have established induced pluripotent stem cell (iPSC)-derived macrophages and characterized these in comparison with primary cells. The plan is to build lung-mimetic multicellular models for studying mycobacterial- and viral infections.

Oudhoff visited the lab of Dr. Bill Horsnell at the University of Cape Town, South Africa, to initiate a collaboration in (lung) infection biology and cellular immunity, and we are increasing our efforts towards performing microbiota studies. In 2020 we published a manuscript about early life intestinal epithelial development. We hope to finalize our work describing the interplay between early life gut epithelium, microbiota, and immune cell development during 2021.

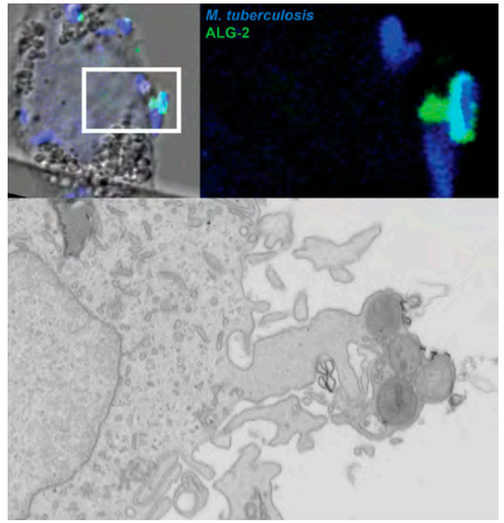
We have performed several studies on genetic risk for sepsis and blood stream infections in HUNT. Recently, we have also explored the genetic risk in skin and soft tissue infections as well as in respiratory tract infections. During 2020 we also set up an international consortium for further studies on the risk of sepsis susceptibility. An important achievement in 2020 was the REK-approval for establishing a general biobank at the intensive care unit. We also established a similar biobank for COVID-19 patients at St Olav's hospital and have initiated OMICs- and mechanistic studies of SARS-CoV2 infection and modulation of anti-viral immunity.

Major achievements 2020

- Published how HIV is recognized by TLR8 in human primary T cells (Meås, Haug et al., *Nature Commun*).
- Published how *M. smegmatis* with a defective type VII secretion system ESX-3 functions as a vaccine vector (Kannan et al., *Frontiers Immunol*).
- Identified the demethylase LSD1 as a critical regulator of postnatal epithelial maturation (Zwiggelaar et al., *Science Advances*).
- Identified the proteome remodeling dynamics of primary human resting and activated CD4+ T cells (Subbannayya et al., *Int J Mol Sci*).
- Contributed to the identification of the lncRNA LUCAT1 as a negative regulator of interferon signaling (Agarwal, S. et al., *Nature Commun*).
- Identified splicing factors and novel post-translational modifications regulating cell death and inflammasome activation in the RIPK1/caspase-8 pathway.
- Summarized findings of importance of caspase-8 in immunity (Orning and Lien, *J Leuk Biol*).
- Developed an organoid imaging screening platform and protocols.
- for iPSC-derived macrophages.
- Established a biobank for COVID-19 patients at St Olav's hospital and protocols for studying SARS-CoV2 infection in vitro.
- Performed genetic studies of patients with blood stream infections (BSI) in the HUNT population and identified that FER rs4957796 (Rogne, T. et al., *Clin Infect Dis*) and the TLR10/1/6 locus (Rogne, T. et al., *Crit Care Med*) was associated with the risk of contracting a BSI.
- A Mendelian randomization study in the HUNT population revealed that high BMI was associated with increased risk of dying from BSI (Rogne et al., *PLOS Medicine*).
- Richard K. Kandasamy received adjunct faculty award from Indian Council of Medical Research.

Ambitions for 2021

- Publish the temporal multiOMICS on host signaling landscape during SARS-CoV2 infection.
- Publish the CRISPR/Cas9 screens for identification of novel host factors of HIV and Influenza A.
- Establish TLR8 ligands as latency-reversal agents for HIV "shock-and-kill" therapy.
- Elucidate the molecular mechanism of novel differentially regulated metabolites identified in a metabolomics screen.
- Publish an unbiased proteomics investigation of THP-1 during PMA differentiation.
- Establish the interplay between early life gut epithelium, microbiota, and immune cell development.
- Publish the development of an organoid imaging screening platform and identification of novel modulators of intestinal epithelial immune effector processes.



Correlative light- and electron microscopy of a macrophage phagocytosing *Mycobacterium tuberculosis*. Plasma membrane disturbances caused by mycobacteria in blue result in calcium influx and recruitment of ALG-2 protein in green. ALG-2 is involved in membrane repair. Photo: Sindre Ullmann.

- Establish the role of extracellular matrix (ECM) control of intestinal repair and gut infection.
- Submit RNA splicing study and effects on RIPK1/caspase-8.
- Investigate new molecules in caspase-1 and caspase-8 cell death, inflammation and inflammasome pathways.
- Publish metformin as host-directed therapy to *M. avium* infection.
- Publish how auto-/paracrine cytokine signaling drive anti-mycobacterial activity.
- Establish high-throughput screen for mycobacterial proteins that influence host processes.
- Establish the function of mycobacterial BlaR and its potential as drug target.
- Finalize project on mycobacterial virulence factors in *Drosophila melanogaster* in collaboration with Germans Trias i Pujol Research Institute in Spain.
- Publish genome-wide association studies with Mendelian randomization in HUNT on the risk of skin and soft tissue infections.
- Recruitment of patients to the general biobank at ICU at St Olav's hospital for studies of sepsis and severe bacterial infections with organ dysfunction.
- Perform genome-wide association studies with Mendelian randomization in HUNT and international cohorts of sepsis patients.
- Study host-pathogen interaction for human isolates of *Staphylococcus aureus* isolates from our BSI-registry in a whole blood model.

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 2020

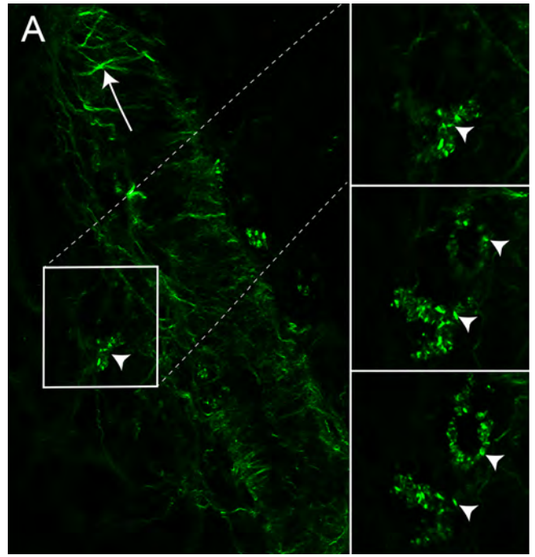
During atherogenesis, cholesterol precipitates into CC in the vessel wall, which trigger plaque inflammation by activating the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome. We have investigated the relationship between CC, complement and NLRP3 in patients with cardiovascular disease. We found that complement contributes to the CC-driven inflammatory responses. Our data imply a positive association between CC- induced complement and NLRP3 activation, both systemically and within the atherosclerotic lesion, with disease severity and instability. The pathogenic loop between complement, CC and NLRP3 inflammasomes may represent a promising target for therapy of atherosclerotic disorders.

We have also worked to delineate how the intracellular complement system (C5) and complement receptor C5aR1 in monocytes and macrophages participate in NLRP3 activation upon phagocytosis of CC. We have obtained data demonstrating the unexpected intracellular formation of the central serum complement activation hubs, the C3/C5 convertases, and identify the C5aR1 as direct modulator of mitochondrial function and, consequently, myeloid cell activity. Together, they suggest that the complosome is a novel contributor to the processes underlying sterile inflammation and that targeting this system could be beneficial in connected diseases such as atherosclerosis.

In the context of atherogenesis two events play a key role in transformation of macrophages into plaque forming foam cells: accumulation of intracellular cholesterol and macrophage cell death induced by modified LDL species. In 2020 we focused on developing and validating a series of assays that are suitable for high throughput screening. As a result, we can now monitor and quantify the rate and extent of cholesterol uptake at a single cell level. Furthermore, we are able to reproducibly model lipid driven macrophages cell by application of lysophospatidylcholine micelles. In the coming year we will use these assays in whole genome CRISPR screens to identify novel regulators of pro-atherogenic signaling.

PRR activation and cholesterol accumulation is shown to be strongly associated to development of placental dysfunction at the two sites of direct maternal-fetal interaction; the uterine wall lining called the decidua and the fetal cell layer covering the placenta. Direct maternal-fetal cellular communication and atherotic lesions with foam cells have been defined in the uterine wall. Inflammasome NLRP3 and cholesterol accumulation have been revealed as particularly important players at the maternal-fetal interface in preeclampsia. Metabolomic profiling has identified grades of placental dysfunction and maternal serum cytokine profiling is used as sensitive measure of maternal immune activation, for causal classification preeclampsia and fetal growth restriction and novel biomarker selection. Novel maternal preeclampsia risk genes have been revealed in the largest meta-analysis of GWAS data in preeclampsia, performed in the EU FP7 project InterPregGen where we participate with the HUNT Study.

Overall, this work has added novel evidence to the involvement of PRR-mediated inflammation in preeclampsia development and the mechanistic relation to cardiovascular disease, and led to discovery of several underlying inflammatory mechanisms, maternal and fetal genetic risk factors, and novel predictive tools for hypertensive pregnancy disorders.



Cholesterol crystals in the uterine wall (decidua) imaged by second harmonic generation microscopy. The arrow heads indicate cholesterol crystals and the arrow points to collagen fibers. From Silva et al, Frontiers in Immunology 2020. Photo: Gabriela Silva.

In 2020 we also finished the ASSAIL-study recruiting 200 patients with transmural myocardial infarction at OUS (Ullevål and Rikshospitalet) and St Olav's hospital to treatment with the IL-6 blocker tocilizumab or placebo. The main article containing clinical- and MRI-data has been prepared and was accepted in late autumn. A large biobank has been collected and sub-studies on mechanisms of IL-6-blockade have already been planned and several are in progress.

Major achievements 2020

- Published that CC use complement to increase NLRP3 signalling pathways in coronary and carotid atherosclerosis (Niyonzima *et al, EBioMedicine* 2020).
- Identified novel maternal risk genes for preeclampsia that are shared with cardiovascular disease and obesity, based on the HUNT Study and the EU FP7 project InterPregGen (Steinthorsdottir *et al, Nature Communications* 2020).
- Revealed accumulation of cholesterol crystals and NLRP3 activation at the maternal side of the placenta in preeclampsia (Silva *et al, Frontiers in Immunology* 2020).
- Identified a role for TLR3 at the maternal-fetal interface in preeclampsia by novel automated image-based immunohistochemistry quantification method (Gierman et *al, Journal of Leukocyte Biology* 2020).
- Measured sensitive changes in maternal immune status during pregnancy by maternal serum cytokine profiling in large pregnancy cohorts.
- We provided novel insights into the effects of Interleukin 6 antagonism in Non-ST-Segment-Elevation myocardial infarction employing the SOMAscan proteomics platform (George M *et al J Am Heart Assoc.* 2020).

Ambitions for 2021

- Demonstrate that mitochondrial C5aR1 activity in macrophages drives optimal IL-1β production underlying sterile inflammation.
- Explore the systemic effects of a low-calorie restricted diet on leukocytes pattern recognition receptors, thromoboinflammation and cytokines.
- Determine connections between cytokines and weight-loss profiles.
- Use whole genome CRISPR screens to identify novel regulators of pro-atherogenic signallinCombine and correlate data sets for PRR mediated danger response, maternal and fetal vascular malperfusion, and pathological processes such as oxidative stress, at the maternal-fetal interface in preeclampsia and fetal growth restriction.
- Complete extensive profiling of the maternal systemic immune status during pregnancy by measuring serum cytokines in normal and complicated pregnancies.
- Utilize the novel automated image-based immunohistochemistry quantification methods to further identify cell specific maternal-fetal communication.
- Establish causal classification of subgroups of preeclampsia and fetal growth restriction by metabolomic profiling.
- Expanded collection of patient-based biobanks for translational inflammation studies.
- Explore the effect of IL-6 blockade on the cytokine network in patients with ST-elevation myocardial infarction.
- Determine the effect of IL-6 blockade on neutrophil NET production during myocardial ischemia.
- Show that IL-6 blockade increases the myocardial salvage index in patients with an acute myocardial infarctions.

Theme 4:
Molecular mechanisms of inflammatory bowel disease and intestinal regeneration

Theme Manager: Professor Arne Sandvik

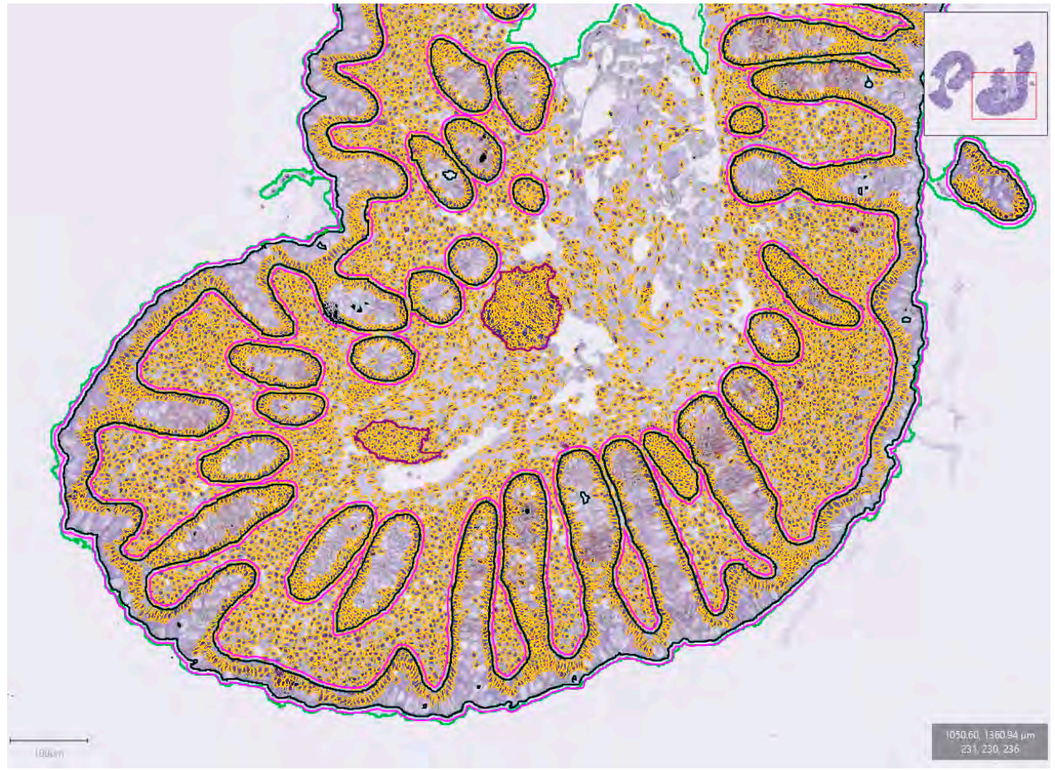
Inflammatory bowel disease (IBD) are chronic diseases arising most likely from an inappropriate inflammatory response to commensal gut microbes. It is a relative lack of in-depth studies of disease mechanisms in human-derived experimental models. This theme studies the IBD inflammatory process and its 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 2020

The research group has continued studying colonic epithelial responses to immunological and physiological signals such as cytokines and chemokines. During 2020 work has also encompassed examining the effect of IBD-approved drugs on inflammation-conditioned organoids to prepare for coming use of organoids as real-life bioassays for clinical use to circumvent the clinical problem of heterogenous response to disease-modifying drugs. This work is being done in a collection of patient-derived colonoids and the model is now being done in a physiological low-oxygen environment rather than in routine incubator conditions. Simultaneously, our work using mouse in vivo and mouse organoid disease models are used to discover new regulators of intestinal epithelial biology in general, but with specific relevance for inflammatory and infectious diseases. Moreover, efforts are being 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. As part of this, longitudinal studies in IBD patients are ongoing to correlate clinical parameters and drug responses with colonoid behavior at the level of the individual patient. This is facilitated by new 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 γδ lymphocytes (Singapore collaboration). Planned visits have been called off due to the coronavirus pandemic but studies are ongoing at the different sites and at NTNU to compensate for this.

Major achievements in 2020

- The CAG project to generate highly refined patient data and material is starting at the turn of the year.
- A prospective intervention study aimed at identifying treatment response and defining the role of NGAL as a biomarker has finished inclusions and is being wrapped up before analyses start.
- A major study on epithelial cell specific gene expression in different inflammatory states of IBD has been completed and is prepared for publication.
- Culture conditions for colonoids have been optimized using physiologically relevant oxygen concentrations and the importance for e.g. chemokine release has been shown.
- Studies on collagenous colitis have identified NGAL as a biomarker for the disease, and contributed to understanding the pathobiology of this disease.
- Studies on the clinically important process of fibrosis in Crohn's disease highlight the role of 5-hydroxytryptamine.
- A study on the discovery of the epigenetic modifier LSD1 as a regulator of early life epithelial development was published.
- A study about the role of smooth muscle cells in intestinal epithelial repair has been submitted and is in revision.



Digital pathology and artificial intelligence – Training of deep learning networks for epithelial segmentation (purple/black lines) and automated quantification of immunepositive cells (pink spots) among all other cell types (yellow circles). Screenshot from QuPath: Henrik P. Sahlin Pettersen.

- Identified the demethylase LSD1 as a critical regulator of postnatal epithelial maturation (Zwiggelaar et al., *Science Advances*).
- Found ISG15 to be secreted from primary intestinal epithelial cells upon proinflammatory stimulation (Østvik et al., *J Crohns Colitis*).
- Identified Aquaporin 8 as a critical regulator of intestinal fluid homeostasis in collageneous colitis (Østvik, Granlund et al., *J Crohns Colitis*).
- Found epithelial serotonin reuptake transporter reduced in the colonic epithelium in active IBD (Jørandli er al., *Am J Physiol*).
- Described mucosa-associated microbiome in ileum in Crohn's disease (Granlund, Røyset, Sandvik et al., *Inflamm Bowel Dis*).

Ambitions for 2021

- Manage the ongoing prospective patient studies to ensure maximally informative data and material.
- Use patient-specific colonoids in prediction of drug responses – personalized medicine.
- Further refine the colonoid model by establishing permanent genetically modified cultures for mechanistic studies.
- Use colonoids together with clinical material to define the role of NGAL in epithelial proliferation and mucosal repair.
- Delineate IBD-relevant immunological mechanisms originating in the epithelial cells during normoxia and hypoxia.
- Further elucidate the role of 5-hydroxytryptamine in the fibrotic process in Crohn's disease.
- 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.

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 may support tumor progression by intrinsic cell mechanisms, and by cross-talks between tumor cells and stroma. The aim of this theme is to understand interactions between tumor cells and the microenvironment at a molecular level.

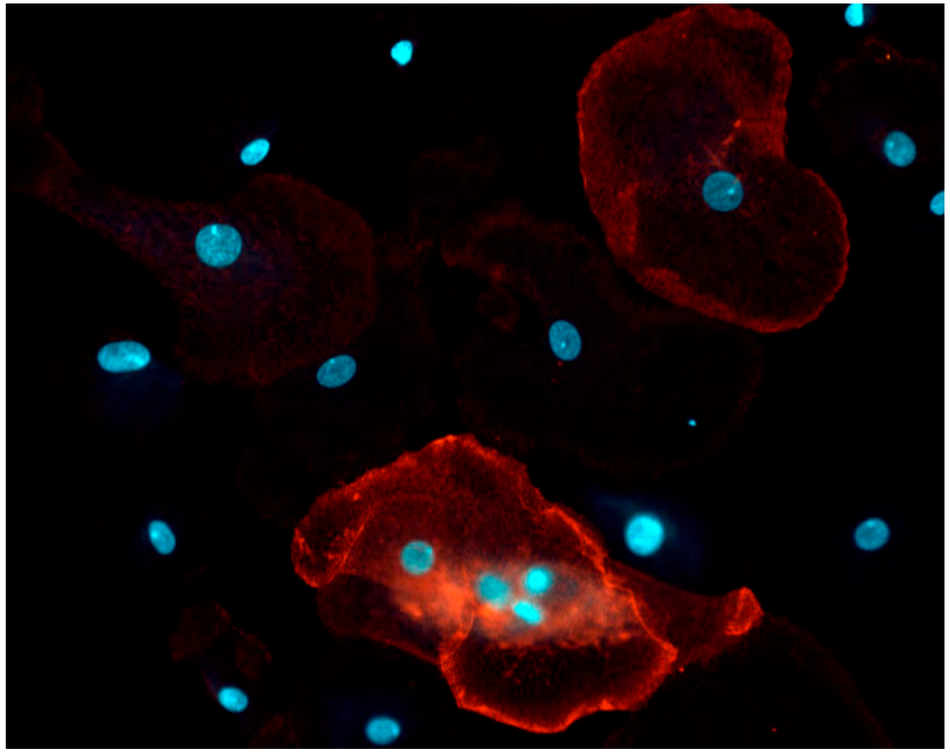
Main activities in 2020

We studied how tumor cells manipulate PRR expression and signaling in the tumor microenvironment, and how this shapes and affects immune cell recruitment and responses. We established models to study neutrophils and plasmacytoid dendritic cells and gained insight into the characteristics of neutrophil polarization states. We published that altered immunoglobulin glycosylation mediate bone loss in multiple myeloma and we studied how altered immunoglobulin glycosylation may influence the activity and function of other cells with FC-gamma receptors. We identified a novel function of IL-32 in myeloma cell survival and proliferation. We mapped the effect of Smac-mimetics in proinflammatory macrophages and discovered that TAK1 regulated important cell survival programs in multiple myeloma. We published that the secretion of IL-6 from cancer cells is controlled through autocrine signaling in the cancer cells of a tumor. We study how this relates to local and systemic alterations in the immune system.

Related to this, we find that peptide-decorated nanoparticles are rapidly engulfed by phagocytes in the blood before these immune cells infiltrate into solid tumors. Innate immune cells infiltrate solid tumors in response to signaling factors secreted from the cancer cells. We find that constitutive oxidative stress signaling in cancer cells may affect the secretome in such a way that it may stimulate local chemotaxis and also affect differentiation in the bone marrow. Thus, cancer cells harboring somatic mutations that cause activation of NRF2 driven oxidative stress responses can control local immunity and cancer progression. In line with this notion, we could patent a 16 transcript, gene expression signature in breast cancer biopsies that predict disease progression. The signature can be used to guide a gentler treatment of breast cancer patients having low-grade, hormone receptor positive tumors.

Major achievements in 2020

- Published a paper on the role of immunoglobulin glycosylation for bone loss in multiple myeloma.
- Published a review paper on the molecular function of IL-32.
- Published a review paper on why myeloma patients loose bone.
- Paper on the effect of Smac-mimetics on osteoclastogenesis was accepted for publication.
- Genetically manipulated expression of discrete chemokines in breast cancer cells and prepared for in vivo tumor formation and metastasis experiment in immunocompetent mouse model.
- Performed gene and protein expression analyses of immune cells isolated from metastatic and non-metastatic cancer.
- Generated supporting data on a patent application for a 16-transcript, oxidative stress-related gene expression signature in breast cancer biopsies. Initiated discussions for licensing.



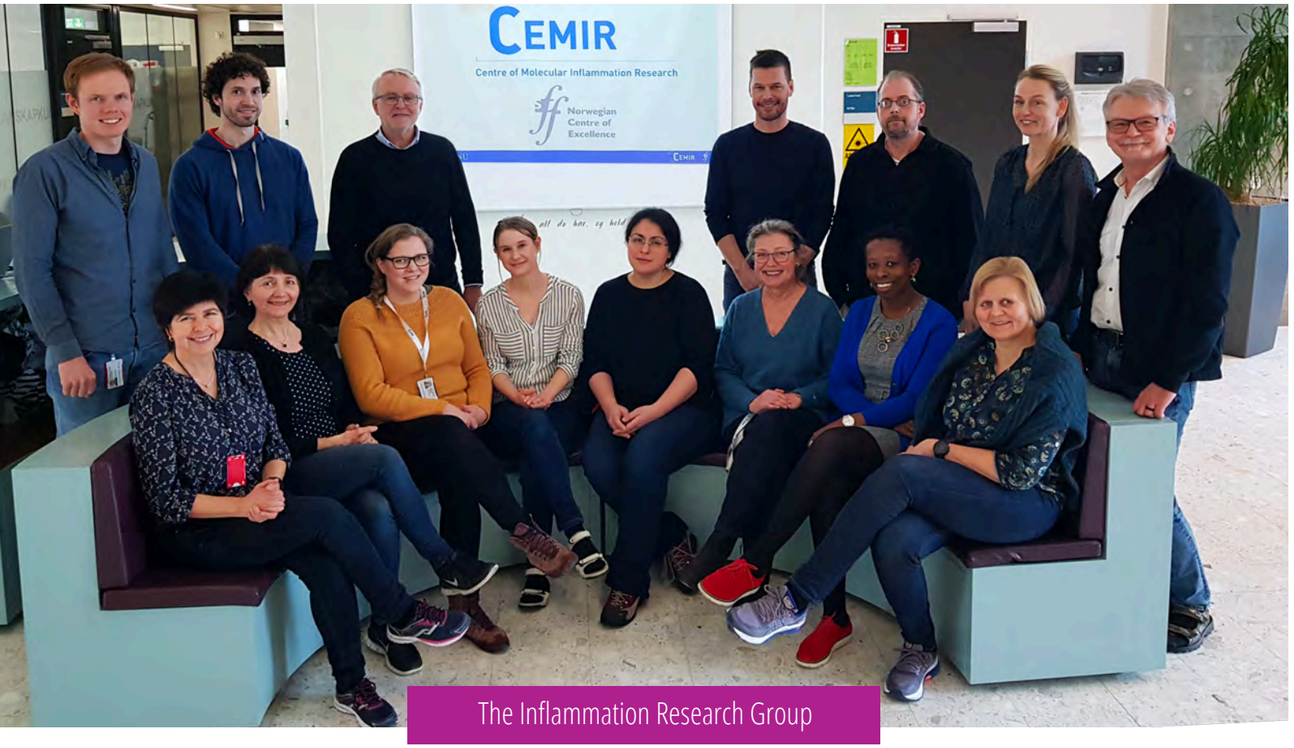
We established a novel EVOS-based osteoclast scoring assay to determine the effect of Smac-mimetics on osteoclastogenesis. Integrin CD51/61 positive multinucleated cells were scored as osteoclasts. Human multinucleated osteoclasts stained for CD51/61 (red) and nucleus (blue, Hoechst 33342).
Photo: Ingrid N. Moen and Kristian Starheim.

- Performed gene and protein expression analyses of immune cells isolated from metastatic and non-metastatic primary breast tumors.
- Established an in vitro model at CEMIR for studying human neutrophil polarization.
- Characterized human neutrophil polarization using this model and identified new markers for neutrophil polarization.
- Two PhD students defended their thesis.
- Published a paper on the role of immunoglobulin glycosylation for bone loss in multiple myeloma (Westhrin et al., *Blood* 2020).
- Published a review paper on why myeloma patients loose bone (Borset et al., *Blood Rev.* 2020).

Ambitions for 2021

- Publish findings on how PRR activation in cancer cells induces neutrophil recruitment and polarization.
- Publish a manuscript describing the novel oxidative stress related gene expression signature for breast cancer prognostics.
- Unravel putative interactions between constitutive oxidative stress response in cancer cells and tumor immunity.
- Define true NRF2 controlled genes in breast cancer cells by combining RNA sequencing of depleted cells with ChIPseq of NRF2.
- Mechanistically describe how IL-6 may stimulate catabolic processes in muscle cells.
- Define the interdependence of autophagy and interferon responses in cancer cells and solid tumours with the focus on local immunity.
- Determine why immunoglobulin glycosylation is reduced in multiple myeloma.
- Publish paper on the effect of TAK1-inhibitors in multiple myeloma.
- Publish a review paper on the molecular function of IL-32.
- Publish a paper on the effect of Smac-mimetics on osteoclastogenesis.

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. These three instruments are installed and well-integrated in the CEMIR laboratories. The inflammation Research Group is collaborating with other CEMIR groups (Flo, Kandasamy and Bjørkøy) 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 (Sandvik, Damås and Iversen).

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 and P. Aukrust, 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 signaling compounds and local metabolite levels to regulate inflammation in normal tissues and solid tumors. Development and progression of solid tumors is influenced by the infiltrating immune cells. So-called immunologically cold tumors display clear signs of local immune suppression, develop more aggressively and respond poorly to treatment. On the other side, immunologically "hot-tumors" show favorable prognosis and better responses to therapy. We, and many others, aim to find new ways to convert the local immune environment in solid tumors 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 signaling proteins in all cell types, including cancer cells. Activation of the Type I Interferon response is a sign of a "hot" tumor. 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 tumors is controlled by autophagy. For these studies, we combine data from tumors from an immunocompetent mouse model with data mining in large databases of tumor biopsy and clinical information. The aim is to explore the idea that autophagy is a selective cellular mechanism involved in the regulation of tumor immunity. Innate immune cells like macrophages and neutrophils are important in solid tumors to initiate and maintain the immune microenvironment. Tumors dominated by anti-inflammatory macrophages and immature neutrophils indicates poor prognosis and limited effect of therapy. We search for causal activities for these innate immune cells as identify targets to reprogramming the immune environment. Formation of such macrophages depends on the macrophage specific receptor CSF1R. In a multidisciplinary collaboration, we explore novel CSF1R inhibitors as candidates for reprogramming tumor immunity. The aim of these studies is to find compounds that can reprogram the local immune microenvironment. Autophagy is also a way to mobilize amino acids and other nutrients during starvation. Degradation of cellular proteins is strictly controlled. Cancer cachexia is a severe complication that affect many cancer patients and is characterized by dramatic loss of muscle proteins. We have found that serum from cancer patients contain autophagy-inducing bioactivities and that this activity associates with loss in body weight. Our data demonstrate that IL-6 secreted from cancer cells cause loss of muscle mass in animal models. Our focus now is on how IL-6 released from the tumor may affect the immune system in ways that stimulate autophagy and reduced energy levels in muscle cells. 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

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 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 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, Runa Heimstad, Trine Moholdt and Bård Kulseng at St. Olavs Hospital, Tone Bathen at NTNU, and Raymond Redline at Cleveland Medical Center. The Research Group is partner in the 12-partner EU 7FP project InterPregGen coordinated by Professor Linda Morgan at University of Nottingham, unravelling genetic risk factors for preeclampsia. 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 2020, the group counted 10 persons; Professor Iversen, one post doc, four PhD students, two MD PhD students, one MD student and one Staff Engineer. Two PhD students completed their thesis in 2020.

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 IBD 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 was significantly strengthened in late 2019, when the group was granted CAG (Clinical Academic Group) status by the Faculty of Medicine and Health Sciences in collaboration with the Central Norway Health Authority. Work is cross-diciplinary, including cell biologists and molecular biologists in addition to clinicians and gastrointestinal pathologists. One of the two IBD group leaders is also the scientific head of the faculty Genomics Core Facility, and is experienced within transcriptome analysis and bioinformatics. Excellent experimental animal facilities, also for genetically modified mice, are available.

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), University of Linköping (Linköping, Sweden) and Institute of Health Research (FISABIO) (Valencia, Spain).

The Bone Disease 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 aim to understand the molecular mechanisms for 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 novel human-mouse scaffold model developed in the laboratory of Anton Martens, the Netherlands. This model allows for a reconstruction of a human hematopoietic environment in scaffolds that are subsequently implanted in immune compromised mice. This model allows for 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. From March 2020 we are part of the newly established clinical academic group (CAG) for multiple myeloma research in Central Norway and we also collaborate closely with the Nordic Myeloma Study Group

The group is led by professor Therese Standal and currently consists of four PhD students, two post doctors, a researcher and a technician.

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 smooth muscle cells, contribute to tissue repair and immunity by secreting so-called 'niche' factors.

We cannot do this work alone, and fortunately we have a range of collaborators for our different research lines that contribute to 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 Glasgow, UK) and Kathryn Else (University of Manchester, UK) on different intestinal helminth infection models. We rely on the expertise of Dr. Toshiro Sato (Keio University, Tokyo, Japan) for human organoid models, and we collaborate with Dr. Kim Jensen (The BRIC, Copenhagen, Denmark) to study fetal and regenerative intestinal epithelium. Finally, for our epigenetic studies we work together with Dr. John Arne Dahl, (Oslo University Hospital, Norway).

This group started in 2016, is led by Dr. Menno Oudhoff, and in 2020 consisted of 4 Postdocs, 3 PhD students, 1 MSc student, and 1 Research Assistant. We hope two of our PhD students will graduate in 2021, and one postdoc has finalized their studies in December 2020 to become an academic librarian. We are looking forward to see what previous trainees will do in the future. In 2020, we published our first study (Zwiggelaar et al, 2020), and we are revising four other manuscripts that were deposited on the bioRxiv server. We hope 2021 will be a very 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. New or improved treatments for infectious diseases are urgently needed, but hampered by an incomplete understanding of microbial virulence and host responses underlying disease pathology.

Our primary research focus is the molecular host defense mechanisms involved in immunity to mycobacteria, HIV and SARS-CoV2 and virulence strategies employed by these pathogens to parasitize host cells. Intracellular trafficking, compartmentalized pattern recognition receptor signaling, host cell killing, and nutrient metabolism are central processes currently inve-stigated in our lab. Most of our work is on the cell biology of infection or in mouse infection models, but we do collaborate with clinicians on translational research projects. We believe our basic research strategy may contribute to revealing new therapeutic targets and adjunct host-directed therapies, as well as in vaccine development.

The Research Group is led by Trude H. Flo and includes five more research scientists, one post doc, four PhD students, two medical research students and three master students. We have developed expertise, methods and tools to study HIV, mycobacteria, SARS-CoV2 and the host innate and adaptive immune defenses both in vitro/ex vivo in human primary cells and cell lines, and in vivo in mice. We just established induced pluripotent stem cell (iPSC)-derived macrophages and will continue with building lung-mimetic multicellular models for studying infections.

We have strains of *Mycobacterium tuberculosis* (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 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. We collaborate closely with the systems inflammation group (R Kandasamy), the inflammation group (T Espevik, JK Damås) and with CEMIR affiliated professors E Lien (UMass), D Underhill (Cedars Sinai) and H Stenmark (OUS). We also pioneer the use of Focused Ion-Beam Scanning Electron Microscopy at NTNU Nanolab to perform high resolution imaging of intracellular infections. Central external collaborators are P Bruheim (NTNU, Dept. Biotechnology), A Simonsen (UiO, autophagy), AM D Riise (OUS, TB & HIV), K Tasken (OUS, T-cells), E Rubin (Harvard, mycobacteria), R Brosch (Institut Pasteur, mycobacteria), N Reiling (Research Center Borstel, mycobacteria), K Prasad (Yenepoya University, proteomics), M Lerm (Linkøping University, TB screens), M Niederweis (Univ Alabama, Mtb).

The Systems Inflammation Research Group

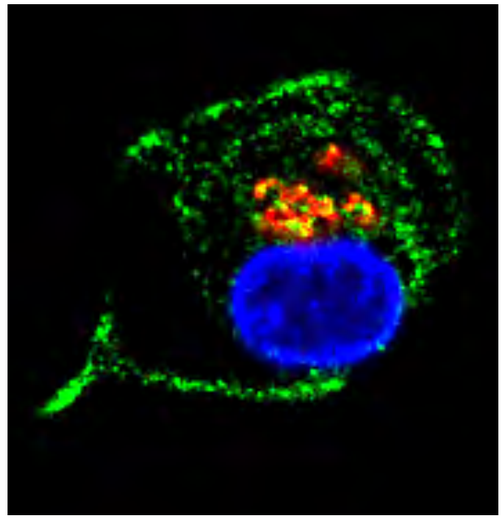
Infectious diseases and inflammatory disorders are major contributors to the global burden of disease, thereby having a huge socio-economic impact. Decades of research have unraveled the arsenal of mechanisms by which the host immune system detects an invading microbe and elicit an innate immune response 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 succination) 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.

The research group led by Richard K. Kandasamy currently includes 1 Ph.D. student, 1 Researcher, 1 post-doc and 1 Masters student. 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), André Müller (Center for Molecular Medicine, Vienna, Austria), Rune Linding (University of Copenhagen, Copenhagen, Denmark), 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 inhibit flammatory responses

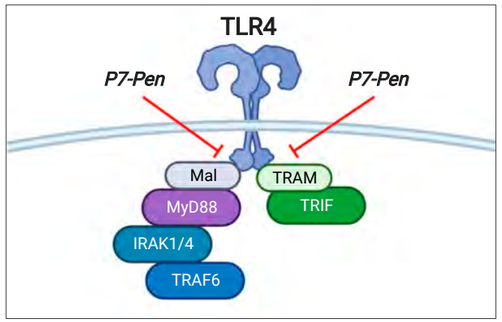


Expression of the SLAMF1 immuno receptor in human monocytes.
Photo: Mariya Yurchenko.

At CEMIR we currently have two innovation strategies for controlling inflammation. The first one is to control inflammation by interfering with the Toll-like receptor signaling pathway.

Microbial as well as sterile inflammation is initiated by pattern recognition. This is the initial and most upstream event for the inflammatory response, which subsequently leads to activation of a broad inflammatory network with release of innumerable of mediators. In the presence of a systemic infection, microbial pathogens and their soluble mediators induce strong inflammatory- and coagulation activation, leading to hypercytokinemia, severe sepsis and septic shock. Despite current treatment strategies and advances in supportive care of critically ill patients, the mortality rate has barely decreased during the past decades. Thus, there is a need for identifying new targets and new strategies for controlling inflammatory responses.

Researchers from CEMIR recently discovered that SLAMF1 protein interacts with several key regulators of TLRs signaling (Yurchenko et al, J Cell Biol 2018). These interactions are crucial for pro-inflammatory cytokines expression in response to activation of both TLR4 and TLR9. Based on this discovery, they developed a strategy to inhibit TLRs-mediated inflammatory response by synthetic peptides derived from SLAMF1 protein.



Inhibition of proteinflammatory cytokines TNF, IL-6, IL-1β and inhibition of INFβ secretion.

SLAMF1 derived drug candidate, target and mode of action

The drug candidate is a peptide composed of 10 amino acids, linked to a cell penetrating peptide (CPP) sequence for effective intracellular delivery. Several CPPs have been successfully tested, and penetratin was chosen for further development. Intracellularly, the peptide blocks the recruitment of crucial adaptor protein Mal/TIRAP and thereby inhibits the formation of the Myddosome complex and TNFα, IL-6, Il-1β and several other pro-inflammatory cytokines secretion. The peptide also directly interacts with the TRIF-Related Adaptor Molecule (TRAM) and inhibits TLR4-mediated expression of IFNβ.

The SLAMF1-derived peptides are currently in pre-clinical stage. The safety and efficacy of the peptides to regulate the cytokine production were thoroughly tested in primary human monocytes, THP-1 cell line and an ex vivo whole blood model. The animal studies in several disease models will be carried out in 2021.

The results show:

- The effect of peptides is reversible, concentration dependent, with working concentration in 5-20 μM range
- Peptides inhibit pro-inflammatory cytokines (TNFα, Il-1β, IL-6) and IFNβ expression and secretion mediated by TLR4 and TLR9 as well as TLR8-mediated IFNβ expression
- Peptides do not alter TLR2 and IL-1R-mediated signaling
- Peptides inhibit uptake of G+ and G- bacteria

The anti-inflammatory peptides and their use are covered by pending patent application filed in 2020.

Given broad inhibitory activity towards several TLRs and low toxicity, SLAMF1-derived peptides have high potential for efficient inhibition of inflammation in patients with different acute and chronic inflammatory conditions as well as overall decrease of inflammation-driven complications.

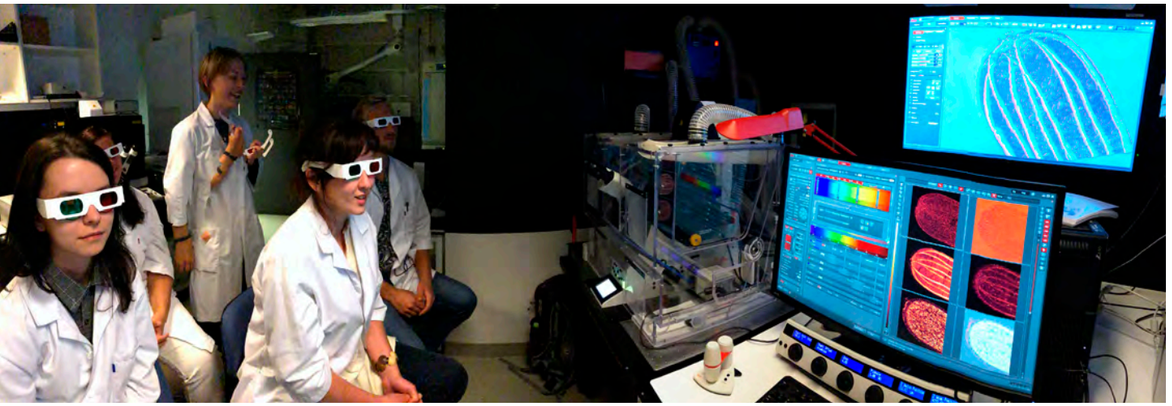
Colony stimulating factor 1 receptor inhibitor

The other innovation strategy is to control inflammation by interfering with the colony stimulating factor 1 receptor (CSF1R). The tyrosine kinase receptor CSF1R, specifically expressed on monocyte-derived cells, is crucial for differentiation and survival of macrophages including bone-degrading osteoclasts. CSF1R activity is also important for pro-tumorigenic macrophages in solid tumors. Thus, chemical inhibitors of CSF1R may be useful in several conditions driven by hyperactive macrophages such as bone diseases and cancer. Organic chemists at NTNU (Hoff/Sundby) have designed and synthesized novel compounds that inhibit CSF1R activity with potency and specificity that is superior to current alternative inhibitors in enzyme assays. At CEMIR, the autophagy group headed by Geir Bjørkøy has developed a novel screening approach to evaluate the compounds in CSF1 induced signaling in macrophages. The best candidates are further tested for administration, distribution, metabolism and excretion (ADME) at the Max-Planck, Lead Discovery Center (LDC) in Dortmund. We are now testing lead drug candidates for efficacy and toxicity in rat and mouse models. Based on these analyses, the best compounds will now be tested in animal models of bone disease and cancer.

A gene signature for personalized treatment of cancer patients

The cellular oxidative stress response coordinated by the gene regulator NRF2 is important in cellular stress responses and inflammatory conditions. NRF2 is frequently hyper-activated by somatic mutations in several forms for solid cancers. In breast cancer, somatic mutations in the NRF2 pathway is rare but a high frequency of breast cancer biopsies show elevated transcription of a discrete subset of NRF2 controlled genes. Based on this observation, we have deduced a NRF2 related gene expression signature of 16 transcripts in RNA from biopsies. Rise in this NRF2 signature strongly correlates with poor prognosis for all breast cancer subtypes, including patients with early-stage, hormone receptor positive tumors. Using several large breast cancer cohorts, the NRF2 signature is a strong and independent predictor of outcome compared to Pam50 ROR gene expression signature recently introduced for breast cancer prognostics. We also find that the NRF2 adds predictive strength to Pam50 ROR when these are combined. The aim is that the NRF2 signature can aid in the identification of patients that can be treated more carefully than current regimes. A patent application is approved, and we are discussing with international actors how this approach may support future personalized treatment of breast cancer patients.

CEMIR-USE OF THE IMAGING CORE FACILITY



From a course where CMIC contributed with instruments, technical assistance and presentations. The microscope at the picture is a Leica SP8 STED. Photo: Bjørnar Sporsheim.

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.

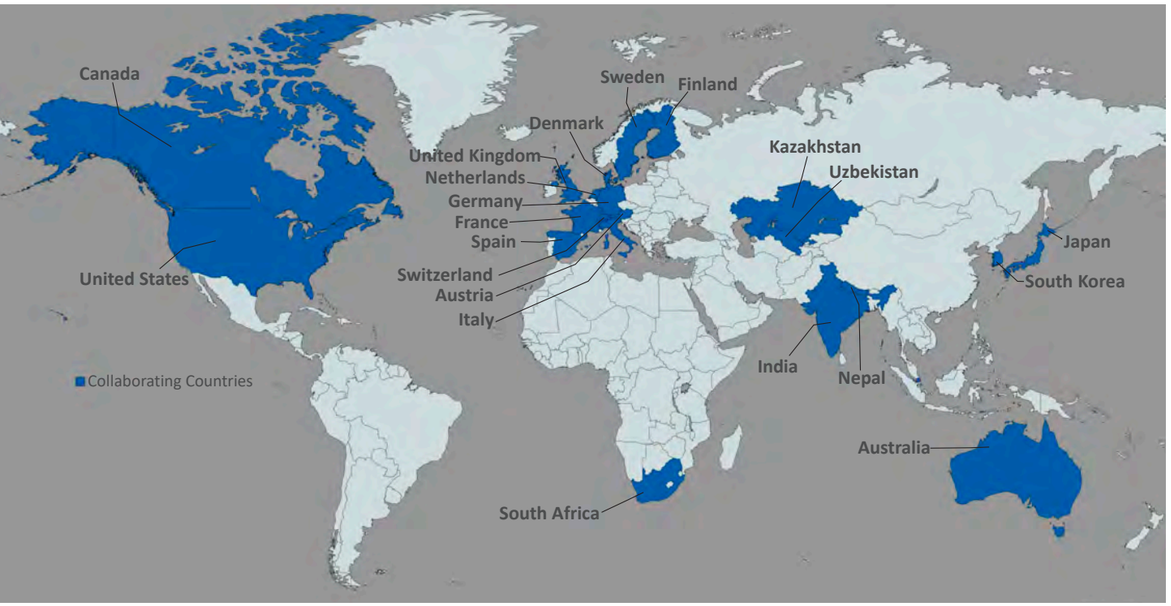
Researchers and students at CEMIR have access to a multitude of different imaging techniques, for live cell studies as well as imaging of fixed cells and tissue preparations. These instruments are all part of the Cellular and Molecular Imaging Core Facility, CMIC, at Faculty of Medicine, NTNU, www.ntnu.edu/mh/cmic. 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 two years this microscope has become one of the most used imaging system with 37 unique users, the majority of which are 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 array detector can also be used in "fast" mode for high speed, high resolution live cell imaging. The instrument is otherwise well equipped with an incubator system for controlled temperature and CO2 environment. The Zeiss Zen Connect software can be used to combine and correlate data from other microscopes and modalities, such as electron microscopy for a better understanding of your samples.

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. High content imaging is also possible on a Zeiss TIRF III fluorescence microscope equipped with a new Hamamatsu Orca-Fusion camera. Rapid and initial fluorescence screening is now available on rebuilt Zeiss Axiovert 200M with a new PCO camera plus a CoolLED light source.

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.

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 and Scotland.

English is our daily working and teaching language
37 % of the CEMIR staff is international, representing 17 different countries. All CEMIR seminars, guest lectures and courses at master- and PhD level are held in English.

CEMIR and the cooperation with clinical departments in 2020

Therese Standal og Tobias S. Slørdahl.

Our goal is to develop new therapeutic approaches and biomarkers for inflammatory and infectious diseases through basic research on molecular innate immune responses. We investigate inflammatory pathways in various infections, 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. To achieve this goal in translational medicine, we have established a close collaboration between CEMIR and St. Olav's hospital in several projects. Several papers from 2020 includes analyses of clinical materials, further establishing the clinical relevance of basis inflammatory processes. We have published several studies using clinical samples from both biobanks and interventional studies in several infectious diseases, cardiovascular and gastrointestinal diseases, cancers and preeclampsia. Researchers from CEMIR participated in the ASSAIL-study where patients with ST-elevation myocardial infarction received the IL-6 blocker tocilizumab or placebo. Late autumn 2020 we also got approval for establishing a general biobank at the intensive care unit (ICU) at St Olav's hospital. This will allow future studies for sepsis and severe infections with organ failure as well as acute coronary syndromes. 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 have now been announced 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, with Tobias S. Slørdahl, St. Olav's hospital, and Therese Standal, CEMIR, as leaders. A CAG is an academic clinical research group, which consist of researchers and clinicians from the NTNU and St Olav's hospital. This will be achieved a strong professional network between CEMIR, St Olav's hospital and the rest of the health region. Another major achievement in the cooperation between clinical departments and CEMIR was the founding of the Colorectal Cancer (CRC) Center at IKOM. The goal of CRC is to identify novel approaches to improve colorectal cancer diagnostics and management. Group leader Menno Oudhoff and researcher Nadra Jesmine Nilsen at CEMIR has contributed to the establishment of a new Colorectal Cancer (CRC) Research Center together with gastrosurgeons and oncologists at St Olav's hospital. The aim is to is to lay ground where research groups at CEMIR will find good opportunities for collaborations at the CRC center, and to ensure this, Oudhoff is one of the theme leaders on development and early detection of CRC.

COMPLETED PHDs in 2020
for the degree of Philosophiae Doctor

Siv Boon Mundal
defended her thesis *Pathological processes in the uterine wall decidua in preeclampsia and fetal growth restriction*
January 13., 2020.
Her supervisors have been Professor Ann-Charlotte Iversen (NTNU), Professor II Ganesh Acharya (University of Tromsø), and Professor Line Bjørge (University of Bergen).

Kristin Roseth Aass
defended her thesis *The role of IL-32 in multiple myeloma*
September 23., 2020.
Her supervisors have been Professor Therese Standal and postdoc Marita Westhrin (both NTNU).

Vlado Kovcic
defended his thesis *New players in an old game: Role of immunoglobulins in the pathogenesis of multiple myeloma*
April 23., 2020.
His supervisors have been Professor Therese Standal and postdoc Marita Westhrin (both NTNU).

Camilla Izabel Wolowczyk
defended her thesis *Novel pathways to metastasis of breast cancer*
December 4., 2020.
Professor Geir Bjørkøy has been her supervisor, while General Manager of PROMEC Lars Hagen, Professor Anne Mary Bofin and Researcher Toril Holien have been co-supervisors (all NTNU).

Gabriela Brettas Silva
defended her thesis *Inflammation by pattern recognition receptors in the uterine wall decidua and the placenta of normal and preeclamptic pregnancies*
June 18., 2020.
Her supervisors have been Professor Ann-Charlotte Iversen, Marie Hjelmseth Aune (NTNU), and researcher Liv Thorsen (Haukeland Universitetssykehus).

Helene Kolstad Skovdal
defended her thesis I*mmunoregulatory roles of chemokines and epithelium in inflammatory bowel disease – CCL20 in mucosa, human colonoids and peripheral blood mononuclear cells*
December 14., 2020.
Her supervisors have been Professor Arne Kristian Sandvik, researcher Atle van Beelen Granlund and Professor Jan Kristian Damås (ann NTNU).

ABOUT CEMIR

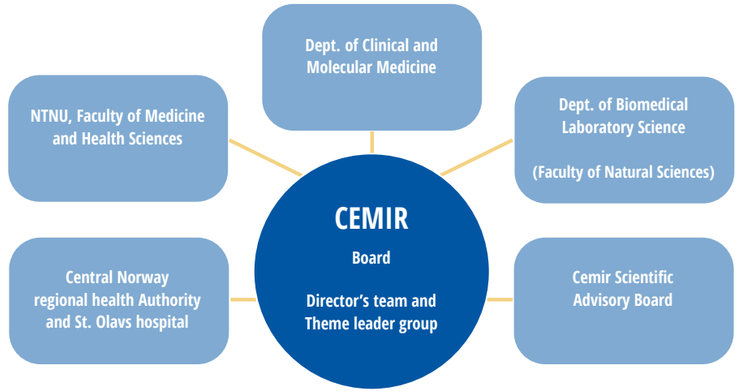
CEMIR's host department is Department of Clinical and Molecular Medicine at the Faculty of Medicine and Health Sciences, NTNU. In addition, CEMIR has two main partners: Department of Biomedical Laboratory Science at the Faculty of Natural Sciences hosting the Autophagy group, and The Central Norway Regional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

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

CEMIR board
One board meeting was held in 2020.
From 2018 the board members have been:
- Torstein Baade Rø – (Board chairman)
  Head of Dep. of Clinical and Molecular Medicine, 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,
  B & M Gates Foundation



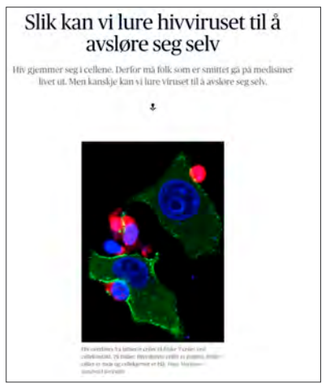
The function of SAB is to review the scientific progress of the Centre and to give guidance to future research directions.

SCIENCE COMMUNICATION AND OUTREACH ACTIVITY

Tom Eirik Mollnes and coworkers' findings about covid-19-infections were described in the media, e.g. by Dagens Medisin. The study has been published in PNAS.

Trude H. Flo was interviewed by NRK about their latest findings on how the tuberculosis bacterium kills host cell. The research has been published in Nat. Comm., and was also described by NRK viten and Norwegian SciTech News.

Jan Kristian Damås and coworkers were interviewed by Aftenposten about their research published in PLoS Medicine.



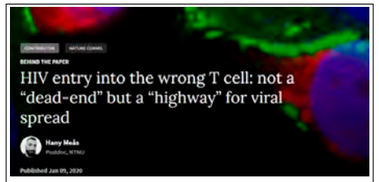
A publication in Nat. Comm. by Hany Meås and coworkers received a lot of attention in the media, e.g GEMINI, Aftenposten Viten, Norwegian SciTechNews and several international newspapers.

Gabriela Silva and the InPreg group's findings published in Front. Immunol. were presented at NRK.

Adresseavisen described how Jan Kristian Damås and coworkers at NTNU and St. Olavs hospital are working to try to find medicines that might help corona-patients.

The Bone disease group's publication in Blood received a lot of publicity, e.g. at NRK and Gemini. Therese Standal has also been interviewed by "I margen" about their research.

Blogs and podcasts:



Hany Meås had a "behind the paper" blog in **Nature Research Micro community** about their HIV paper.

En faktablogg om medisin og helse ved NTNU
NTNU Medisin og helse har flyttet til ny adresse:
www.ntnu.no/blogger/helse

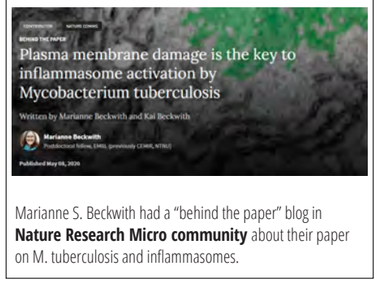
Forskning ◇ forskning ◇ NTNUhealth

Hvordan vi oppdaget en ny mekanisme i immunceller for å vekke HIV virus som ligger i dvale

av @NTNUhelse | 26. februar 2020

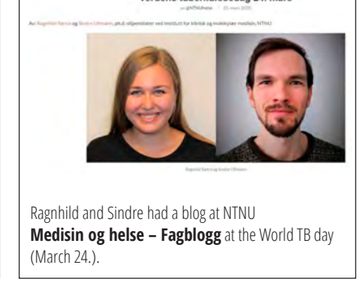
Markus Haug blogged about the same paper **@NTNUhelse.**

Hany also contributed to a podcast about HIV at **Diagnose** (St. Olav), in which he talks about the findings in their recent publication in Nat. Comm.



Marianne S. Beckwith had a "behind the paper" blog in **Nature Research Micro community** about their paper on M. tuberculosis and inflammasomes.

Ragnhild Sætra and Sindre Ullmann blogged about the same paper **@NTNUhelse.**



Ragnhild and Sindre had a blog at NTNU **Medisin og helse – Fagblogg** at the World TB day (March 24.).

Bonusepisode:
Koronavaksinen – forskning i superfart

Koronavaksinen er rett rundt hjørnet. Hvem bør få den først – og hvor mange må ta den – og vil en vaksine egentlig løse problemet?

Jan Kristian Damås. Foto: Nils Heldal

Publisert 27.11.2020 / Sist oppdatert 30.11.2020

Jan Kristian Damås talked about the corona-situation in a podcast at **Diagnose**.

Despite of the pandemic, CEMIR researchers have contributed with presentations at some conferences and meetings, such as:

- Keystone Symposium Tuberculosis
- «Innate immunity in cardiovascular disease» meeting
- Blodkreftforeningens seminar om myelomatose
- The annual IBA meeting
- AMR-BRIDGE workshop «The need for new antibiotics»
- GAK - Gløshaugen Akademiske Klubb

GUEST LECTURES IN 2020

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.

During the pandemic, this aim has been maintained by arranging the guest lectures at zoom.

April 27th,
Professor Harald Stenmark,
University of Oslo and
Oslo University Hospital and
affiliated professor at CEMIR:
Regulation of cellular membrane dynamics.

June 17th,
Dr. Charlotte Odendall,
King's College London, UK:
Interferon: tug of war between host and pathogen.

June 17th,
Researcher Xavier Lahaye,
Institut Curie, Paris, France:
cGAS-STING, HIV and genetic instability.

October 26th,
Professor Eicke Latz,
University of Bonn and affiliated professor at CEMIR:
Unbiased analysis of mediators of metaflammation.

October 28th,
Professor David Underhill,
Cedars-Sinai, Los Angeles, USA,
and affiliated professor at CEMIR:
Innate and Adaptive Immune Responses to Malassezia in Crohn's Disease.

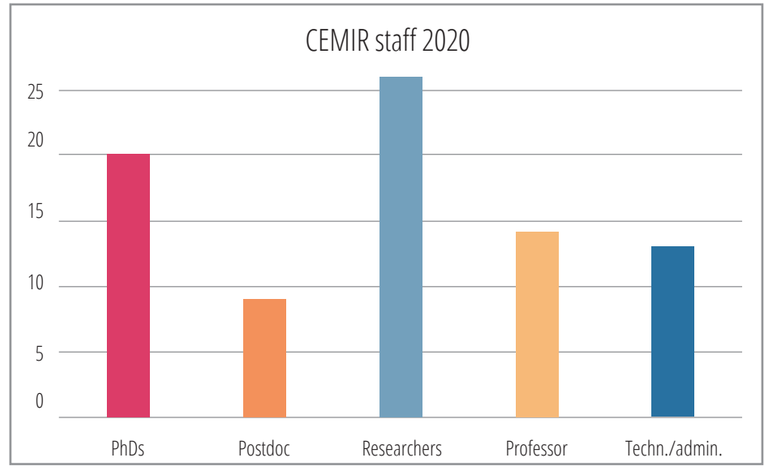
November 13th,
Professor Tom Eirik Mollnes,
Oslo University Hospital and affiliated professor at CEMIR: *Treatment of complement-mediated diseases in the clinic – from rare diseases to corona pandemics?*

November 17th,
Dr. John Brumell,
University of Toronto, Canada:
Mechanisms of cell-to-cell spread by Listeria monocytogenes.

CEMIR STAFF 2020

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 2020, 67 scientific staff members, 14 technicians, 21 students and one administrative coordinator were associated with the Centre.



Name		Position	Nationality	Research group
Aass	Kristin Roseth	Postdoctor	Norway	Bone disease
Alonso	Mara	Researcher	Spain	Regeneration
Andersen	Sonja	Staff engineer	Norway	Support group
Bakke	Siril Skaret	Postdoctor	Norway	Inflammation
Bjørkøy	Geir	Professor	Norway	Autophagy
Brigant	Benjamin	Postdoctor	France	Inflammation
Buene	Glenn	Staff engineer	Norway	Bone disease
Bugge	Marit	Researcher	Norway	Bone disease
Cemalovic	Ena	PhD	Bosnia and Herzegovina	Inflammation
Damaas	Jan Kristian	Professor	Norway	Inflammation
Diez	Alberto	Postdoctor	Spain	Regeneration
Dragset	Marte Singsås	Researcher	Norway	MYCOVIR
Egeberg	Kjartan	Staff engineer	Norway	Support group
Espevik	Terje	Professor	Norway	Inflammation
Fitzgerald	Kate	Professor II	UK	
Flo	Trude Helen	Professor	Norway	MYCOVIR
Giambelluca	Miriam	Postdoctor	Spain	Autophagy
Gidon	Alexandre	Researcher	France	MYCOVIR
Gierman	Lobke	Researcher	Netherlands	InPreg
Granlund	Atle van Beelen	Researcher	Norway	IBD
Gravastrand	Caroline	PhD	Norway	Inflammation
Haug	Markus	Researcher	Germany	MYCOVIR
Husebye	Harald	Researcher	Norway	Inflammation
Iversen	Ann-Charlotte	Professor	Norway	InPreg
Johansson	Ida	Researcher	Norway	Autophagy
Kandasamy	Richard Kumaran	Associate professor	India	Systems inflammation
Kastnes	Martin	PhD	Norway	Bone disease
Kim	Hera	PhD	South-Korea	Systems inflammation
Kojen	June Frengen	Staff engineer	Norway	Support group
Lamsal	Apsana	PhD	Norway	Autophagy
Latz	Eicke	Professor II	Germany	
Lian	Tone Aksnes	PhD	Norway	MYCOVIR
Lien	Egil	Professor II	Norway	
Lindholm	Håvard Takle	PhD	Norway	Regeneration
Louet	Claire	Staff engineer	France	Support group
Ma	Qianli	Postdoctor	China	Bone disease
Marstad	Anne	Staff engineer	Norway	Support group
Mediaas	Sindre Dahl	PhD	Norway	MYCOVIR
Meås	Hany Zakaria	Postdoctor	Egypt	MYCOVIR
Moen	Siv	Researcher	Norway	Bone disease
Moen	Ingrid Nyhus	PhD	Norway	Autophagy

Mollnes	Tom Eirik	Professor II	Norway	
Nedal	Tonje	PhD	Norway	Bone disease
Nilsen	Nadra	Researcher	Norway	Inflammation
Nilsen	Kaja Elisabeth	PhD	Norway	Inflammation
Niynzima	Nathalie	Researcher	Burundi	Inflammation
Nonstad	Unni	Staff engineer	Norway	Support group
Ostrop	Jenny	Researcher	Germany	Regeneration
Oudhoff	Menno	Researcher	Netherlands	Regeneration
Parmar	Naveen	Postdoctor	India	Regeneration
Pettersen	Kristine	Postdoctor	Norway	Autophagy
Pinto	Sneha Maria	Postdoctor	India	Systems inflammation
Rakner	Johanne Johnsen	PhD	Norway	InPreg
Rokstad	Anne Mari	Researcher	Norway	Inflammation
Ryan	Liv	Staff engineer	Norway	Support group
Sandvik	Arne	Professor	Norway	IBD
Selvik	Linn-Karina	Staff engineer	Norway	Support group
Serra	Ignacio Catalan	Postdoctor	Spain	IBD
Silva	Gabriela Brettas	Researcher	Brazil	InPreg
Skjesol	Astrid	Researcher	Norway	Inflammation
Spanjers	Roos	Staff engineer	Netherlands	Regeneration
Sporsheim	Bjørnar	Staff engineer	Norway	Support group
Standal	Therese	Professor	Norway	Bone disease
Starheim	Kristian K.	Researcher	Norway	Inflammation
Steigedal	Magnus	Researcher	Norway	MYCOVIR
Steinkjer	Bjørg	Staff engineer	Norway	Support group
Stenmark	Harald	Professor II	Norway	
Stenvik	Jørgen	Researcher	Norway	Inflammation
Stokkeland	Live	PhD	Norway	InPreg
Strand	Trine Aakvik	Head of administration/ Staff engineer	Norway	
Subbannayya	Yashwanth	Researcher	India	Systems inflammation
Sundan	Anders	Professor	Norway	
Sætra	Ragnhild	PhD	Norway	MYCOVIR
Tande	Erlend	PhD	Norway	Inflammation
Ullmann	Sindre	PhD	Norway	MYCOVIR
Underhill	David	Professor II	USA	
Vik	Randi	Staff engineer	Norway	Support group
Vornewald	Pia	PhD	Germany	Regeneration
Wolowczyk	Camilla	PhD	Norway	Autophagy
Yurchenko	Mariia	Researcher	Ucraine	Inflammation
Zwiggelaar	Rosalie	PhD	Netherlands	Regeneration

CEMIR SCIENTIFIC PUBLICATIONS 2020

Aasarød, Kristin Matre; Waldum, Helge; Stunes, Astrid Kamilla; Sandvik, Arne Kristian; Flatberg, Arnar; Mjønes, Patricia; Syversen, Unni; Bakke, Ingunn; Fossmark, Reidar.
Gastric Corpus Mucosal Hyperplasia and Neuroendocrine Cell Hyperplasia, but not Spasmolytic Polypeptide-Expressing Metaplasia, Is Prevented by a Gastrin Receptor Antagonist in H+/K+ATPase Beta Subunit Knockout Mice. *International Journal of Molecular Sciences* 2020 ;Volum 21.(3)
NTNU STO

Aass, Kristin Roseth; Kastnes, Martin; Standal, Therese.
Molecular interactions and functions of IL-32. *Journal of Leukocyte Biology* 2020 NTNU STO

Agarwal, Shiuli; Vierbuchen, Tim; Ghosh, Sreya; Chan, Jennie; Jiang, Zhaozhao; Kandasamy, Richard Kumaran; Ricci, Emiliano; Fitzgerald, Katherine A..
The long non-coding RNA LUCAT1 is a negative feedback regulator of interferon responses in humans. *Nature Communications* 2020 ;Volum 11. s.6348
NTNU

Beckwith, Kai Sandvold; Beckwith, Marianne Sandvold; Ullmann, Sindre; Sætra, Ragnhild Sofie Ragnhildstveit; Kim, Hae Lin; Marstad, Anne; Åsberg, Signe Elisabeth; Strand, Trine Aakvik; Haug, Markus; Niederweis, Michael; Stenmark, Harald Alfred; Flo, Trude Helen.
Plasma membrane damage causes NLRP3 activation and pyroptosis during Mycobacterium tuberculosis infection. *Nature Communications* 2020 ;Volum 11:2270. s.1-18
NTNU UiO

Berg, Leif Kyrre; Goll, Rasmus; Fagerli, Erik; Ludviksen, Judith K; Fure, Hilde; Odd Sverre, Moen; Sørbye, Sveinung; Mollnes, Tom Eirik; Florholmen, Jon.
Intestinal inflammatory profile shows increase in a diversity of biomarkers in irritable bowel syndrome. *Scandinavian Journal of Gastroenterology* 2020 ;Volum 55.(5) s.537-542
HELSEHELG NLSH NTNU OUS UiO UiT UNN

Chaban, Viktoriia; Clarke, Gerard; Skandsen, Toril; Islam, Rakibul; Einarsen, Cathrine Elisabeth; Vik, Anne; Damås, Jan Kristian; Mollnes, Tom Eirik; Håberg, Asta; Pischke, Soeren.
Systemic inflammation persists the first year after mild traumatic brain injury: Results from the Prospective Trondheim Mild Traumatic Brain Injury Study. *Journal of Neurotrauma* 2020 ;Volum 37.(19) s.2120-2130
NLSH NTNU OUS STO UiO UiT

Choudhury, Asmita; Bullock, Daniel; Lim, Arlene; Argemi, Josepmaria; Ørning, Mathias Pontus; Lien, Egil; Bataller, Ramon; Mandrekar, Pranoti.
Inhibition of HSP90 and Activation of HSF1 Diminish Macrophage NLRP3 Inflammasome Activity in Alcohol-Associated Liver Injury. *Alcoholism: Clinical and Experimental Research* 2020 ;Volum 44.(6) s.1300-1311
NTNU

Ehrnstrøm, Birgitta; Kojen, June Frengen; Giambelluca, Miriam; Ryan, Liv; Moen, Siv Helen; Hu, Zhenyi; Yin, Hang; Mollnes, Tom Eirik; Damås, Jan Kristian; Espevik, Terje; Stenvik, Jørgen.
TLR8 and complement C5 induce cytokine release and thrombin activation in human whole blood challenged with Gram-positive bacteria. *Journal of Leukocyte Biology* 2020 ;Volum 107.(4) s.673-683
NLSH NTNU OUS STO UiO UiT

Escudero-Hernandez, Celia; Münch, Andreas; Østvik, Ann Elisabet; Granlund, Atle van Beelen; Koch, Stefan.
The water channel aquaporin 8 is a critical regulator of intestinal fluid homeostasis in collagenous colitis. *Journal of Crohn's and colitis* 2020;Volum 14.(7) s.962-973
NTNU STO

George, Marc J; Kleveland, Ola; Garcia-Hernandez, Jorge; Palmen, Jutta; Lovering, Ruth; Wiseth, Rune; Aukrust, Pål; Engmann, Jorgen; Damås, Jan Kristian; Hingorani, Aroon D; Gullestad, Lars; Casas, Juan P; Ueland, Thor.
Novel Insights Into the Effects of Interleukin 6 Antagonism in Non-ST-Segment-Elevation Myocardial Infarction Employing the SOMAscan Proteomics Platform. *Journal of the American Heart Association* (JAHA) 2020 ;Volum 16.(12) s.1-21
NTNU OUS STO UiO UiT

Gierman, Lobke; Silva, Gabriela; Pervaiz, Zahra; Rakner, Johanne Johnsen; Mundal, Siv Boon; Thaning, Astrid Josefin; Nervik, Ingunn; Elschot, Mattijs; Mathew, Seema; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Iversen, Ann-Charlotte.
TLR3 expression by maternal and fetal cells at the maternal-fetal interface in normal and preeclamptic pregnancies. *Journal of Leukocyte Biology* 2020 s.1-11
HAUKELAND NTNU STO UiB

Grinde, Dina Mikhailovna; Øverland, Torstein; Lima, Kari; Schjalm, Camilla; Mollnes, Tom Eirik; Abrahamsen, Tore G.
Complement Activation in 22q11.2 Deletion Syndrome. *Journal of Clinical Immunology* 2020 ;Volum 40.(3) s.515-523
AHUS NLSH NTNU OUS UiO UiT

Holter, Jan Cato; Pischke, Soeren; de Boer, Eline; Lind, Andreas; Jenum, Synne; Holten, Aleksander Rygh; Tonby, Kristian; Barratt- Due, Andreas; Sokolova, Marina; Schjalm, Camilla; Chaban, Viktoriia; Kolderup, Heidi Anette; Tran, Trung; Tollefsrud Gjølberg, Torleif; Skeie, Linda Gail; Hesstvedt, Liv; Ormaasen, Vidar; Fevang, Børre; Austad, Cathrine; Muller, Karl Erik; Fladeby, Cathrine; Holberg- Petersen, Mona; Halvorsen, Bente; Müller, Fredrik; Aukrust, Pål; Dudman, Susanne Gjeruldsen; Ueland, Thor; Andersen, Jan Terje; Lund-Johansen, Fridtjof; Heggelund, Lars; Dyrhol-Riise, Anne Ma; Mollnes, Tom Eirik.
Systemic complement activation is associated with respiratory failure in COVID-19 hospitalized patients. *Proceedings of the National Academy of Sciences of the United States of America* 2020 ;Volum 117.(40) s.25018-25025
NLSH NTNU OUS UiB UiO UiT VV

Hovland, Anders; Retterstøl, Kjetil; Mollnes, Tom Eirik; Halvorsen, Bente Evy; Aukrust, Pål; Lappegård, Knut Tore.
Anti-inflammatory effects of non-statin low-density lipoprotein cholesterol-lowering drugs: an unused potential?. *Scandinavian Cardiovascular Journal* 2020 s.1-7
NLSH NTNU OUS UiO UiT

Høvik, Lise Husby; Gjeilo, Kari Hanne; Lydersen, Stian; Solligård, Erik; Damås, Jan Kristian; Gustad, Lise Tuset.
Use of peripheral venous catheters in two Norwegian hospitals.. *Tidsskrift for Den norske legeforening* 2020
HNT NTNU STO

Jørandli, Jonas Woll; Thorsvik, Silje; Skovdahl, Helene Kolstad; Kornfeld, Benedikt; Sæterstad, Siri; Gustafsson, Björn; Sandvik, Arne Kristian; Granlund, Atle van Beelen.
The serotonin reuptake transporter is reduced in the epithelium of active Crohn's disease and ulcerative colitis. *American Journal of Physiology - Gastrointestinal and Liver Physiology* 2020 ;Volum 319.(6) s.G761-G768
NTNU STO

Jørgensen, Marthe Jøntvedt; Holter, Jan Cato; Christensen, Erik; Schjalm, Camilla; Tonby, Kristian; Pischke, Soeren; Jenum, Synne; Skeie, Linda Gail; Nur, Sarah; Lind, Andreas; Opsand, Hanne; Enersen, Tone Burvald; Grøndahl, Ragnhild; Hermann, Anne; Dudman, Susanne Gjeruldsen; Müller, Fredrik; Ueland, Thor; Mollnes, Tom Eirik; Aukrust, Pål; Heggelund, Lars; Holten, Aleksander Rygh; Dyrhol-Riise, Anne Ma.
Increased interleukin-6 and macrophage chemoattractant protein-1 are associated with respiratory failure in COVID-19. *Scientific Reports* 2020;Volum 10.
NLSH NTNU OUS UiB UiO UiT VV

Kannan, Nisha; Haug, Markus; Steigedal, Magnus; Flo, Trude Helen.
Mycobacterium smegmatis Vaccine Vector Elicits CD4+ Th17 and CD8+ Tc17 T Cells With Therapeutic Potential to Infections With Mycobacterium avium. *Frontiers in Immunology* 2020 ;Volum 11.
NTNU STO

Keshari, Ravi Shankar; Silasi, Robert; Popescu, Narcis Ioan; Regmi, Girija; Chaaban, Hala; Lambris, John D.; Lupu, Cristina; Mollnes, Tom Eirik; Lupu, Florea.
CD14 inhibition improves survival and attenuates thrombo-inflammation and cardiopulmonary dysfunction in a baboon model of Escherichia coli sepsis. *Journal of Thrombosis and Haemostasis* 2020 ;Volum 19.(2) s.429-443
NLSH NTNU OUS UiO UiT

Kleineidam, Luca; Chouraki, Vincent; Prochnicki, Thomasz; van der Lee, Sven J.; Madrid-Márquez, Laura; Wagner-Thelen, Holger; Karaca, Ilker; Weinhold, Leonie; Wolfsgruber, Steffen; Boland, Anne; Martino Adami, Pamela V.; Lewczuk, Piotr; Popp, Julius; Brosseron, Frederic; Jansen, Iris E.; Hulsman, Marc; Kornhuber, Johannes; Peters, Oliver; Berr, Claudine; Heun, Reinhard; Frölich, Lutz; Tzourio, Christophe; Dartigues, Jean-François; Hüll, Michael; Espinosa, Ana; Hernández, Isabel; de Rojas, Itziar; Orellana, Adelina; Valero, Sergi; Stringa, Najada; van Schoor, Natasja M.; Huisman, Martijn; Scheltens, Philip; Rüther, Eckart; Deleuze, Jean- Francois; Wiltfang, Jens; Tárraga, Lluís; Schmid, Matthias; Scherer, Martin; Riedel-Heller, Steffi; Heneka, Michael T.; Amouyel, Philippe; Jessen, Frank; Boada, Mercè; Maier, Wolfgang; Schneider, Anja; González-Pérez, Antonio; van der Flier, Wiesje M.; Wagner, Michael; Lambert, Jean-Charles; Holstege, Henne; Sáez, Eugenia; Latz, Eicke; Ruiz, Agustin; Ramirez, Alfredo.
PLCG2 protective variant p.P522R modulates tau pathology and disease progression in patients with mild cognitive impairment. *Acta Neuropathologica* 2020 ;Volum 139.(6) s.1025-1044
NTNU

Lipcsey, Miklos; Tenhunen, Jyrki; Pischke, Soeren; Kuitunen, Anne; Flaatten, Hans; De Geer, Lina; Sjölin, Jan; Frithiof, Robert; Chew, Michelle S.; Bendel, Stepani; Kawati, Rafael; Larsson, Anders; Mollnes, Tom Eirik; Tønnessen, Tor Inge; Rubertsson, Sten.
Endotoxin removal in septic shock with the Alteco LPS Adsorber was safe but showed no benefit compared to placebo in the double-blind randomized controlled trial - the Asset Study. Shock 2020 ;Volum 54.(2) s.224-231
HAUKELAND NLSH NTNU OUS UiO UiT

Macpherson, Magnhild Eide; Hov, Johannes Espolin Roksund; Ueland, Thor; Dahl, Tuva Børresdatter; Kummen, Martin; Otterdal, Kari; Holm, Kristian; Berge, Rolf Kristian; Mollnes, Tom Eirik; Trøseid, Marius; Halvorsen, Bente; Aukrust, Pål; Fevang, Børre; Jørgensen, Silje Fjellgård.
Gut microbiota-dependent trimethylamine N-oxide associates with inflammation in common variable immunodeficiency. *Frontiers in Immunology* 2020 ;Volum 11.
NLSH NTNU OUS UiB UiO UiT

Magupalli, Venkat Giri; Negro, Roberto; Tian, Yuzi; Hauenstein, Arthur V.; Caprio, Giuseppe Di; Skillern, Wesley; Deng, Qiufang; Ørning, Mathias Pontus; Alam, Hasan B.; Maliga, Zoltan; Sharif, Humayun; Hu, Jun Jacob; Evavold, Charles L.; Kagan, Jonathan C.; Schmidt, Florian I.; Fitzgerald, Katherine A.; Kirchhausen, Tom; Li, Yongqing; Wu, Hao.
HDAC6 mediates an aggresome-like mechanism for NLRP3 and pyrin inflammasome activation. *Science* 2020 ;Volum 369.(6509) s.1-16
NTNU

Magupalli, Venkat Giri; Negro, Roberto; Tian, Yuzi; Hauenstein, Arthur V.; Di Caprio, Giuseppe; Skillern, Wesley; Deng, Qiufang; Ørning, Mathias Pontus; Alam, Hasan B.; Zoltan, Maliga; Sharif, Humayun; Hu, Jun Jacob; Evavold, Charles L.; Kagan, Jonathan C.; Schmidt, Florian I.; Fitzgerald, Katherine A.; Kirchhausen, Tom; Li, Yongqing; Wu, Hao.
HDAC6 mediates an aggresome-like mechanism for NLRP3 and pyrin inflammasome activation. *Science* 2020 ;Volum 369.(6510) Suppl. eaas8995.
NTNU

Martinez-Hackert, Erik; Sundan, Anders; Holien, Toril.
Receptor binding competition: A paradigm for regulating TGF- family action. *Cytokine & growth factor reviews* 2020 s.1-16
NTNU STO

Meås, Hany Zakaria; Haug, Markus; Beckwith, Marianne Sandvold; Louet, Claire; Ryan, Liv; Hu, Zhenyi; Landskron, Johannes; Nordbø, Svein Arne; Tasken, Kjetil; Yin, Hang; Damås, Jan Kristian; Flo, Trude Helen.
Sensing of HIV-1 by TLR8 activates human T cells and reverses latency. *Nature Communications* 2020 ;Volum 11:147. s.1-16
NTNU OUS STO UiO

Mjelle, Robin; Aass, Kristin Roseth; Sjursen, Wenche; Hofsli, Eva; Sætrom, Pål.
sMETASeq: combined profiling of microbiota and host small RNAs. *iScience* 2020
NTNU STO

Mollnes, Tom Eirik; Huber-Lang, Markus.
Complement in sepsis — when science meets clinics. *FEBS Letters* 2020 ;Volum 594. (16) s.2621-2632
NLSH NTNU OUS UiO UiT

Niyonzima, Nathalie; Bakke, Siril Skaret; Gregersen, Ida; Holm, Sverre; Sandanger, Øystein; Orrem, Hilde Lang; Sporsheim, Bjørnar; Ryan, Liv; Kong, Xiang Yi; Dahl, Tuva Børresdatter; Skjelland, Mona; Sørensen, Kirsten; Rokstad, Anne Mari A.; Yndestad, Arne; Latz, Eicke; Gullestad, Lars; Andersen, Geir Øystein; Damås, Jan Kristian; Aukrust, Pål; Mollnes, Tom Eirik; Halvorsen, Bente; Espevik, Terje.
Cholesterol crystals use complement to increase NLRP3 signaling pathways in coronary and carotid atherosclerosis. *EBioMedicine* 2020 ;Volum 60:102985. s.1-13
NLSH NTNU OUS STO UiO UiT

Olaisen, Maya; Flatberg, Arnar; Granlund, Atle van Beelen; Røyset, Elin Synnøve; Martinsen, Tom Christian; Sandvik, Arne Kristian; Fossmark, Reidar.
Bacterial Mucosa-associated Microbiome in Inflamed and Proximal Noninflamed Ileum of Patients With Crohn's Disease. *Inflammatory Bowel Diseases* 2020
NTNU STO

Pedersen, Henrik; Jensen, Rasmus K.; Jensen, Jens Magnus B.; Fox, Rachel; Pedersen, Dennis V.; Olesen, Heidi G.; Hansen, Annette G.; Christiansen, Dorte; Mazarakis, Sofia M.M.; Lojek, Neal; Hansen, Pernille; Gadeberg, Trine A.F.; Zarantonello, Alessandra; Laursen, Nick S.; Mollnes, Tom Eirik; Johnson, Matthew B.; Stevens, Beth; Thiel, Steffen; Andersen, Gregers R..
A complement C3–Specific nanobody for modulation of the alternative cascade identifies the C-Terminal domain of C3b as functional in C5 convertase activity. *Journal of Immunology* 2020 ;Volum 205.(8) s.2287-2300
NLSH NTNU OUS UiO UiT

Ponsford, Mark J; Gkatzionis, Apostolos; Walker, Venexia M; Grant, Andrew J; Wootton, Robyn E; Moore, Luke; Fatumo, Segun; Mason, Amy M; Zuber, Verena; Willer, Christen; Rasheed, Humaira; Brumpton, Ben Michael; Hveem, Kristian; Damås, Jan Kristian; Davies, Neil Martin; Åsvold, Bjørn Olav; Solligård, Erik; Jones, Simon; Burgess, Stephen; Rogne, Tormod; Gill, Dipender.
Cardiometabolic traits, sepsis and severe covid-19: a Mendelian randomization investigation. *Circulation* 2020 ;Volum 142.(18) s.1791-1793
HNT NTNU STO

Radulovic, Maja; Stenmark, Harald Alfred.
LRRK2 to the rescue of damaged endomembranes. *EMBO Journal* 2020 ;Volum 39.(18) Suppl. e106162. s.1-3
NTNU OUS UiO

Rahman, Jubayer; Singh, Parul; Merle, Nicolas; Niyonzima, Nathalie; Kemper, Claudia.
Complement's favourite organelle-Mitochondria?. *British Journal of Pharmacology* 2020
NTNU

Rogne, Tormod; Damås, Jan Kristian; Flatby, Helene Marie; Åsvold, Bjørn Olav; DeWan, Andrew; Solligård, Erik.
The Role of FER rs4957796 in the Risk of Developing and Dying From a Bloodstream Infection: A 23-Year Follow-up of the Population-based Nord-Trøndelag Health Study. *Clinical Infectious Diseases* 2020
NTNU STO

Rogne, Tormod; Damås, Jan Kristian; Solligård, Erik; DeWan, Andrew.
Genome-Wide Linkage Analysis of the Risk of Contracting a Bloodstream Infection in 47 Pedigrees Followed for 23 Years Assembled From a Population-based Cohort (the HUNT Study). *Critical Care Medicine* 2020 ;Volum 48.(11) s.1580-1586
NTNU STO

Rogne, Tormod; Solligård, Erik; Burgess, Stephen; Brumpton, Ben Michael; Paulsen, Julie; Pescott, Hallie; Mohus, Randi Marie; Gustad, Lise Tuset; Mehl, Arne; Åsvold, Bjørn Olav; DeWan, Andrew; Damås, Jan Kristian.
Body mass index and risk of dying from a bloodstream infection: A Mendelian randomization study. *PLoS Medicine* 2020 ;Volum 17.(11)
HNT NTNU STO

Shahini, Negar; Schjalm, Camilla; Nilsson, Per; Holt, Margrethe Flesvig; Øgaard, Jonas; Lien, Egil; Ahmed, Muhammad Shakil; Attramadal, Håvard; Aukrust, Pål; Yndestad, Arne; Mollnes, Tom Eirik; Louwe, Maria Cornelia.
Complement component C3 and the TLR co-receptor CD14 are not involved in angiotensin II induced cardiac remodelling. *Biochemical and Biophysical Research Communications - BBRC* 2020 ;Volum 523.(4) s.867-873
NLSH NTNU OUS UiO

Sharifi, Sina; Islam, Mohammad Mirazul; Sharifi, Hannah; Islam, Rakibul; Nilsson, Per; Dohlman, Claes H.; Mollnes, Tom Eirik; Paschalis, Eleftherios I.; Chodosh, James.
Sputter deposition of titanium on poly(Methyl methacrylate) enhances corneal biocompatibility. *Translational Vision Science & Technology* 2020 ;Volum 9:41.(13) s.1-14
NLSH NTNU OUS UiO UiT

Silva, Gabriela; Gierman, Lobke; Rakner, Johanne Johnsen; Stødle, Guro; Thaning, Astrid Josefin; Mundal, Siv Boon; Sporsheim, Bjørnar; Elschot, Mattijs; Collett, Karin; Bjørge, Line; Aune, Marie Hjelmseth; Thomsen, Liv Cecilie Vestrheim; Iversen, Ann-Charlotte.
Cholesterol crystals and NLRP3 mediated inflammation in the uterine wall decidua in normal and preeclamptic pregnancies. *Frontiers in Immunology* 2020 ;Volum 11:564712. s.1-12
HAUKELAND NTNU STO UiB

Sofias, Alexandros Marios; Toner, Yohana C.; Meerwaldt, Anu E.; van Leent, Mandy M. T.; Soultanidis, Georgios; Elschot, Mattijs; Gonai, Haruki; Grendstad, Kristin; Flobak, Åsmund; Neckmann, Ulrike; Wolowczyk, Camilla; Fisher, Elizabeth L.; Reiner, Thomas; Davies, Catharina de Lange; Bjørkøy, Geir; Teunissen, Abraham J. P.; Ochando, Jordi; Pérez-Medina, Carlos; Mulder, Willem J. M.; Hak, Sjoerd.
Tumor Targeting by v3-Integrin-Specific Lipid Nanoparticles Occurs via Phagocyte Hitchhiking. *ACS Nano* 2020 ;Volum 14.(7) s.7832-7846
NTNU SINTEF STO

Steinthorsdottir, Valgerdur; McGinnis, Ralph; Williams, Nicholas O.; Stefánsdóttir, Lilja; Thorleifsson, Gudmar; Shooter, Scott; Fadista, João; Sigurdsson, Jon K.; Auro, Kirsi; Berezina, Galina; Borges, Maria-Carolina; Bumpstead, Suzannah; Bybjerg-Grauholm, Jonas; Colgiu, Irina; Dolby, Vivien A.; Dudbridge, Frank; Engel, Stephanie M.; Franklin, Christopher S.; Frigge, Michael L; Frisbaek, Yr; Geirsson, Reynir T.; Geller, Frank; Gretarsdottir, Solveig; Gudbjartsson, Daniel F.; Harmon, Quaker; Hougaard, David Michael; Hegay, Tatyana; Helgadottir, Anna; Hjartardóttir, Sigrún; Jääskeläinen, Tiina; Johannsdottir, Hrefna; Jonsdottir, Ingileif; Juliusdottir, Thorhildur; Kalsheker, Noor; Kasimov, Abdumadjit; Kemp, John P.; Kivinen, Katja; Klungsøyr, Kari; Lee, Wai K; Melbye, Mads; Miedzybrodska, Zosia; Moffett, Ashley; Najmutdinova, Dilbar; Nishanova, Firuza; Olafsdottir, Thorunn; Perola, Markus; Pipkin, Fiona Broughton; Poston, Lucilla; Prescott, Gordon; Saevarsdottir, Saedis; Salimbayeva, Damilya; Scaife, Paula Juliet; Skotte, Line; Staines- Urias, Eleonora; Stefansson, Olafur A.; Sørensen, Karina Meden; Thomsen, Liv Cecilie Vestrheim; Tragante, Vinicius; Trogstad, Lill; Simpson, Nigel A.B.; Aripova, Tamara; Casas, Juan P; Dominiczak, Anna F; Walker, James J.; Thorsteinsdottir, Unnur; Iversen, Ann- Charlotte; Feenstra, Bjarke; Lawlor, Deborah A.; Boyd, Heather Allison; Magnus, Per; Laivuori, Hannele; Zakhidova, Nodira; Syvatova, Gulnara; Stefansson, Kari; Morgan, Linda.
Genetic predisposition to hypertension is associated with preeclampsia in European and Central Asian women. *Nature Communications* 2020 ;Volum 11. s.1-14 FHI
NTNU UiB

Storm, Benjamin; Christiansen, Dorte; Mollnes, Tom Eirik; Nielsen, Erik Waage.
Avoiding ambient air in test tubes during incubations of human whole-blood minimizes complement background activation. *JIM - Journal of Immunological Methods* 2020 ;Volum 487:112876. s.1-5
NORD NLSH NTNU OUS UiO UiT

Subbannayya, Yashwanth; Haug, Markus; Pinto, Sneha; Mohanty, Varshasnata; Meås, Hany Zakaria; Flo, Trude Helen; Prasad, T. S. Keshava; Kandasamy, Richard Kumaran.
The Proteomic Landscape of Resting and Activated CD4+ T Cells Reveal Insights into Cell Differentiation and Function. *International Journal of Molecular Sciences* 2020 ;Volum 22.(1)
NTNU

Tao, Liang; Yi, Yuguo; Chen, Yuxin; Zhang, Haibing; Ørning, Mathias Pontus; Lien, Egil; Jie, Jiapeng; Zhang, Weigao; Xu, Qian; Li, Yang; Ding, Zhao; Wu, Chao; Ding, Qiurong; Wang, Junsong; Zhang, Jianfa; Weng, Dan.
RIP1 kinase activity promotes steatohepatitis through mediating cell death and inflammation in macrophages. *Cell Death and Differentiation* 2020
NTNU

Tøndell, Anders; Wahlstrøm, Sissel Grete; Sponaas, Anne-Marit; Sørhaug, Sveinung; Børset, Magne; Haug, Markus.
Ectonucleotidase CD39 and Checkpoint Signalling Receptor Programmed Death 1 are Highly Elevated in Intratumoral Immune Cells in Non–small-cell Lung Cancer. *Translational Oncology* 2020 ;Volum 13.(1) s.17-24
NTNU STO

Ueland, Nora Lamark; Ludviksen, Judith K; Hellerud, Bernt C; Mollnes, Tom Eirik; Skjeflo, Espen Waage.
Choice of immunoassay to evaluate porcine cytokine levels. Veterinary Immunology and Immunopathology 2020 ;Volum 230:110129. s.1-5 NLSH NTNU OUS UiO UiT

Ueland, Thor; Heggelund, Lars; Lind, Andreas; Holten, Aleksander Rygh; Tonby, Kristian; Michelsen, Annika; Jenum, Synne; Jørgensen, Marthe Jøntvedt; Barratt-Due, Andreas; Skeie, Linda Gail; Nordøy, Ingvild; Fraz, Mai Sasaki Aanensen; Paulsen, Else Quist; Pischke, Soeren; Johal, Simreen Kaur; Hesstvedt, Liv; Bogen, Mette; Fevang, Børre; Halvorsen, Bente; Müller, Fredrik; Bekken, Gry Kloumann; Mollnes, Tom Eirik; Dudman, Susanne Gjeruldsen; Aukrust, Pål; Dyrhol-Riise, Anne Ma; Holter, Jan Cato.
Elevated plasma sTIM-3 levels in patients with severe COVID-19. *Journal of Allergy and Clinical Immunology* 2020 ;Volum 147.(1) s.92-98 NLSH
NTNU OUS UiB UiO UiT VV

Westhrin, Marita; Holien, Toril; Zahoor, Muhammad; Moen, Siv Helen; Buene, Glenn; Størdal, Berit Fladvad; Hella, Hanne; Yuan, Huipin; de Bruijn, Joost D; Martens, Anton; Groen, Richard WJ; Bosch, Fátima; Smith, Ulf; Sponaas, Anne-Marit; Sundan, Anders; Standal, Therese.
Bone Morphogenetic Protein 4 Gene Therapy in Mice Inhibits Myeloma Tumor Growth, But Has a Negative Impact on Bone. *JBMR Plus* 2020 ;Volum 4.(1)
NTNU STO

Westhrin, Marita; Kovcic, Vlado; Zejian, Zhang; Moen, Siv Helen; Nedal, Tonje Marie Vikene; Bondt, Albert; Holst, Stephanie; Misund, Kristine; Buene, Glenn; Sundan, Anders; Waage, Anders; Slørdahl, Tobias Schmidt; Wuhrer, Manfred; Standal, Therese.
Monoclonal immunoglobulins promote bone loss in multiple myeloma. *Blood* 2020
NTNU STO

Yang, Rui; Elsaadi, Samah; Misund, Kristine; Abdollahi, Pegah; Vandsemb, Esten; Moen, Siv Helen; Kusnierczyk, Anna; Slupphaug, Geir; Standal, Therese; Waage, Anders; Slørdahl, Tobias Schmidt; Rø, Torstein Baade; Rustad, Even Holth; Sundan, Anders; Hay, Carl; Cooper, Zachary; Schuller, Alwin G.; Woessner, Richard; Borodowski, Alexandra; Menu, Eline; Børset, Magne; Sponaas, Anne-Marit.
Conversion of ATP to adenosine by CD39 and CD73 in multiple myeloma can be successfully targeted together with adenosine receptor A2A blockade. Journal for ImmunoTherapy of Cancer (JITC) 2020
NTNU STO

Zhang, Jie; Song, Lihong; Pedersen, Dennis V.; Li, Anna; Lambris, John D.; Andersen, Gregers Rom; Mollnes, Tom Eirik; Ma, Ying Jie; Garred, Peter.
Soluble collectin-12 mediates C3-independent docking of properdin that activates the alternative pathway of complement. *eLIFE* 2020 ;Volum 9:e60908. s.1-19
NLSH NTNU OUS UiO UiT

Zwiggelaar, Rosalie; Lindholm, Håvard Takle; Fosslie, Madeleine Lystad; Pedersen, Marianne Terndrup; Ohta, Yuki; Sanchez, Alberto Diez; Martin Alonso, Mara; Ostrop, Jenny; Matano, Mami; Parmar, Naveen; Kvaløy, Emilie; Spanjers, Roos; Nazmi, Kamran; Rye, Morten Beck; Drabløs, Finn; Arrowsmith, Cheryl H; Dahl, John Arne; Jensen, Kim B.; Sato, Toshiro; Oudhoff, Menno.
LSD1 represses a neonatal/reparative gene program in adult intestinal epithelium.
Science Advances 2020 ;Volum 6.(37)
NTNU OUS STO

Ørning, Mathias Pontus; Lien, Egil.
Multiple roles of caspase-8 in cell death, inflammation, and innate immunity.
Journal of Leukocyte Biology 2020
NTNU

Østvik, Ann Elisabet; Svendsen, Tarjei Dahl; Granlund, Atle van Beelen; Doseth, Berit; Skovdahl, Helene Kolstad; Bakke, Ingunn; Thorsvik, Silje; Afroz, Wahida; Walaas, Gunnar Andreas; Mollnes, Tom Eirik; Gustafsson, Björn; Sandvik, Arne Kristian; Bruland, Torunn.
Intestinal epithelial cells express immunomodulatory ISG15 during active ulcerative colitis and Crohn's disease. *Journal of Crohn's and colitis* 2020 ;Volum 14.(7) s.920-934
NLSH NTNU OUS STO UiO UiT

Åsberg, Signe Elisabeth; Mediaas, Sindre Dahl; Marstad, Anne; Ryan, Liv; Louet, Claire; Sporsheim, Bjørnar; Beckwith, Kai Sandvold; Underhill, David; Gidon, Alexandre; Flo, Trude Helen.
Antibiotic treatment routes Mycobacterium avium to phagolysosomes without triggering proinflammatory cytokine production in human macrophages.
Journal of Leukocyte Biology 2020
NTNU

FUNDING AND EXPENDITURES 2020

Funding (1000 NOK)	2020
NTNU	22 947
Research Council of Norway (RCN) – Centre of Excellence grant	14 742
Other RCN funding	15 369
Other public funding	13 748
Other private funding	3 874
International funding	870
Total funding	**71 550**

Expenditures (1000 NOK)	2020
Personnel and indirect costs	55 654
Equipment	53
Other operating costs	15 126
Year result transferred to 2021	717
Total expenditures	**71 550**

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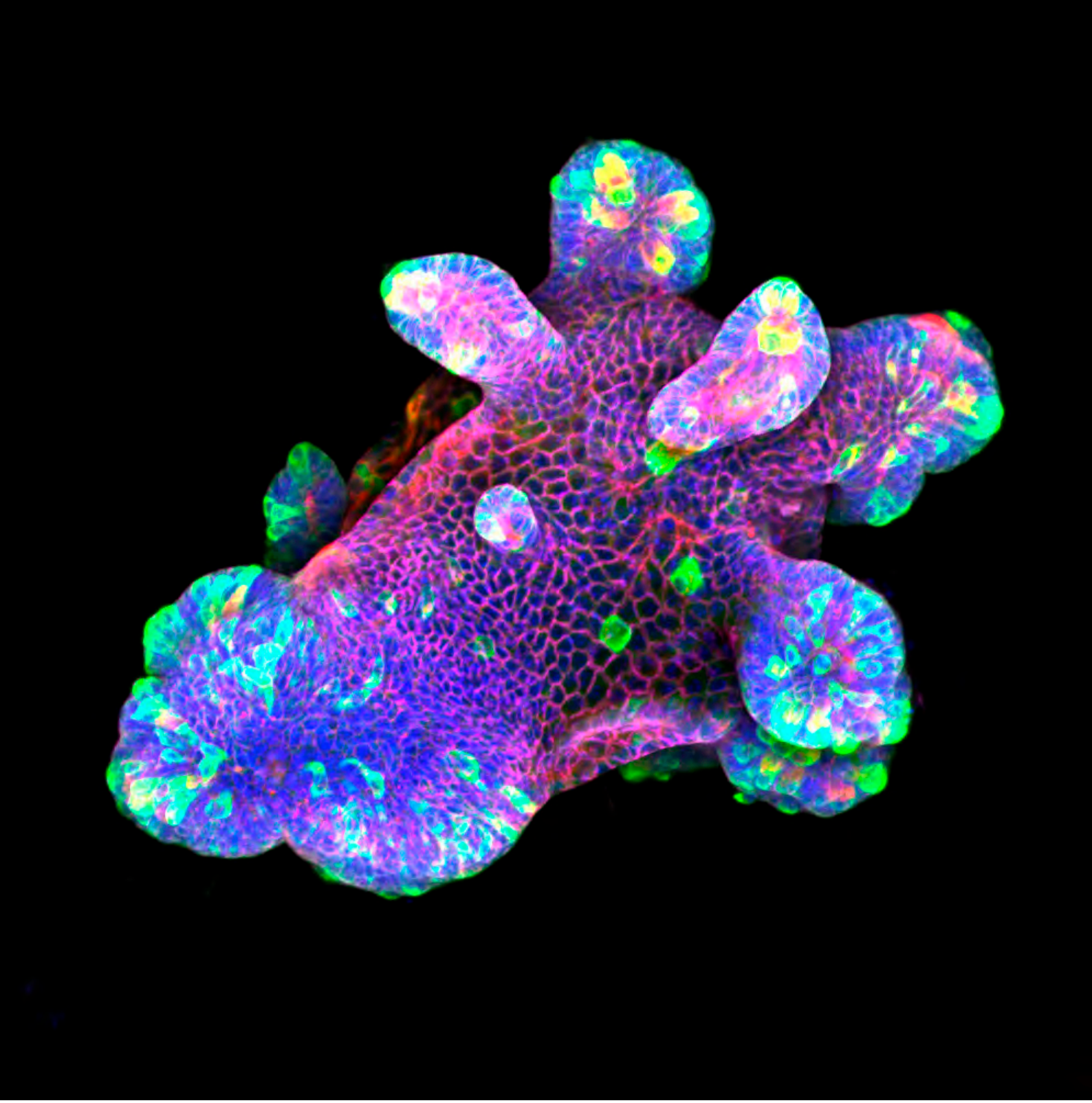
Photo page 42.
Intestinal organoids were treated with IL-22, and in response the antimicrobial protein RELM-beta (green) was induced, Beta-Catenin (purple) and Dapi (blue) were used as counterstain for cell junctions and nuclei respectively. Photo: Naveen Parmar.



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