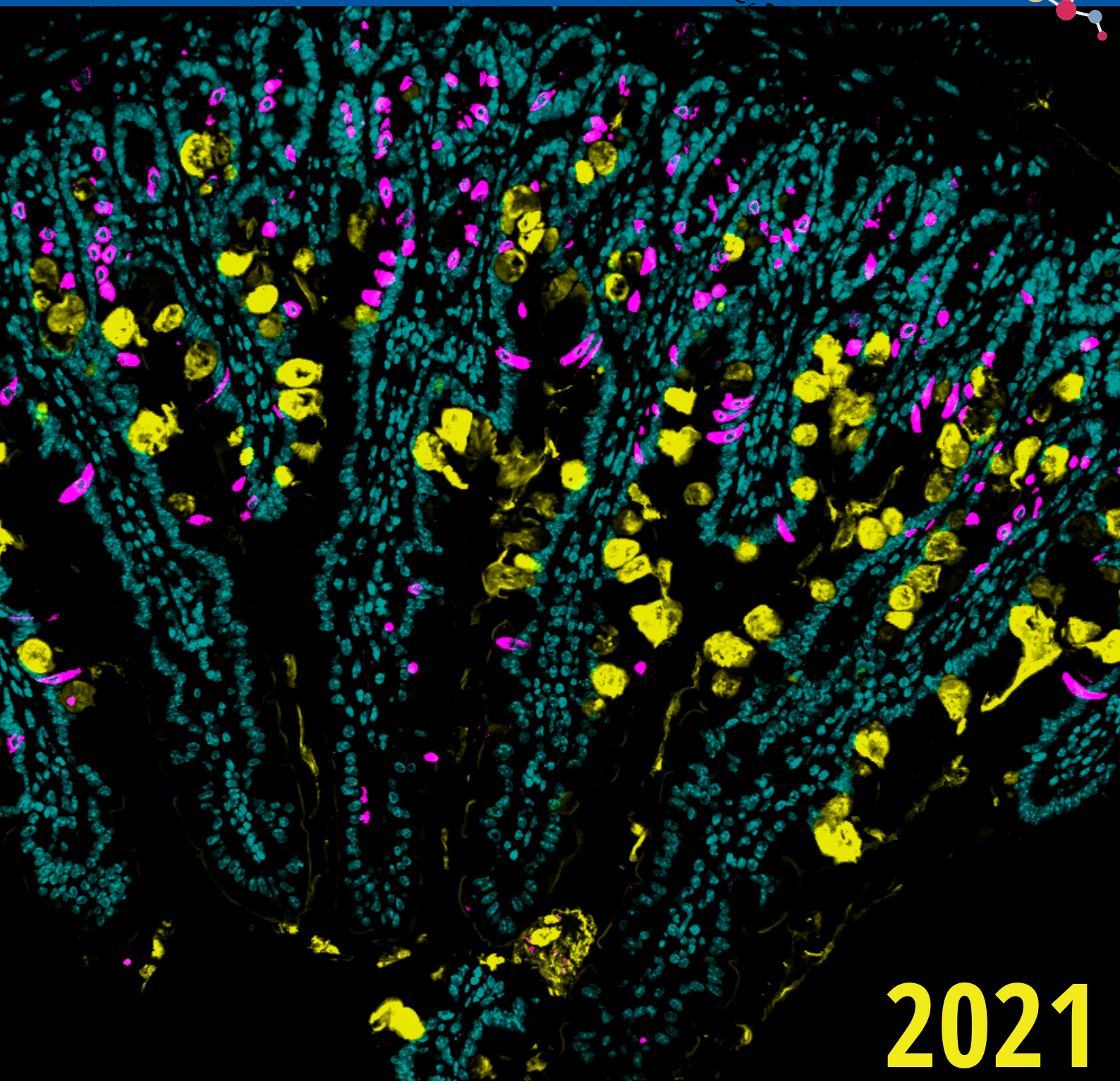

2021

Norwegian Centre of Excellence

The Research Council of Norway

CEMIR

Centre of Molecular Inflammation Research

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Page 1: Section of mouse jejunum infection with a helminth parasite Nippostrongylus brasiliensis.
Hyperplasia of both yellow goblet cells stained with the UEA-I lectin) and magenta tuft cells (expressing doublecortin-like kinase 1) is observed as part of the host immune response to this infection.
Photo: Naveen Parmar and Bjørnar Sporsheim

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.

By the end of 2021 66 scientific staff members, 14 technicians, 13 students and an administrative coordinator were associated with the Centre. In 2017, CEMIR formally became a research unit in the newly established Department of Clinical and Molecular medicine. This will hopefully help us in securing a continuation of the Centre when the RCN funding ends by mid 2023.

Communication is important for maintaining a good work environment and for stimulation of scientific activities. This is done by weekly scientific seminars and monthly Journal Clubs. 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 2021 77 papers have been published. CEMIR researchers have published a total of 531 articles since 2013, several in high quality journals like *Nature Communications, Blood, Science Advances, Science Immunology, Plos Pathogens, Cell, Science, Nature, Nature Immunology, Autophagy, J Cell Biol* and *PNAS*. 41 CEMIR PhD candidates have successfully completed their PhDs. Several of the publications from CEMIR have received front page coverage in journals such as *PNAS, Traffic, Nature Immunology, Science Immunology* and *J Immunol.* Research at CEMIR has also resulted in innovation and submission of a PCT patent application in 2021. We have discovered that peptides from an immunoreceptor are able to inhibit inflammatory responses in macrophages. These peptides have the potential to be developed into novel drugs for treatment of pathological inflammation.

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. 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 2021

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 pyroptotic cell death in macrophage killing. 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, we have investigated several clinical UPEC strains and found one strain driving a particularly high level of cell death. Genome sequencing has identified that this strain encodes an arsenal of bacterial virulence factors modulating the activation of the NLRP3 inflammasome.

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

We have continued studies on TLR8 and TLR2 signalling in human phagocytes. We have also compared the host-pathogen interactions of different GBS isolates in a human whole blood model. Moreover, we have tested whether two genes at a risk-locus for skin and soft tissue infections *(Linc01185* and *SLC12A2, Rogne et al., J. Invest. Dermatol. 2021*) have direct immune regulatory or antibacterial functions in human phagocytes or blood. Lastly, we have initiated the development of an immune functional assay with diluted human blood that can be useful for immune monitoring of patients.

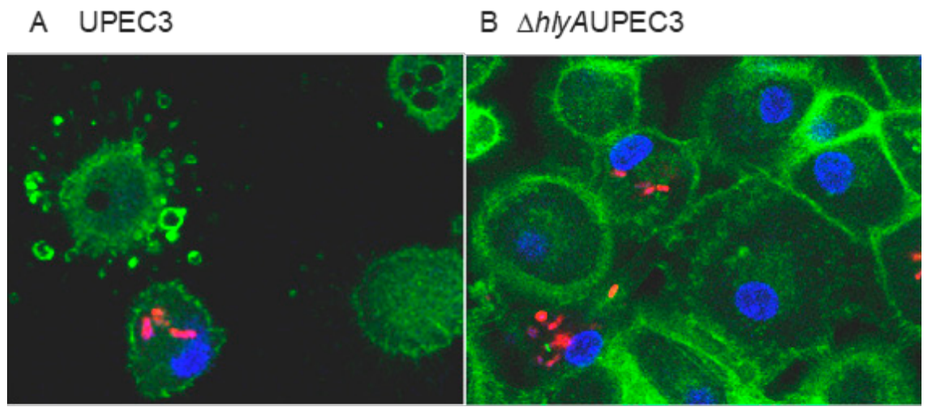


Figure legend: Uropathogenic *E. coli* (UPEC3) induce membrane blebbing and killing of THP-1 macrophages (A). Mutant bacteria lacking the HlyA gene do not kill THP-1 cells (B). Photo: H. Husebye.

Major achievements 2021

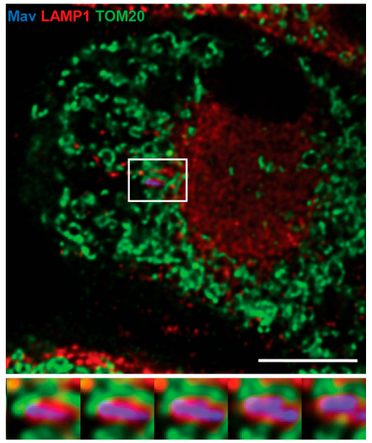
- Constructed several SLAMF1 peptides linked to cell penetrating peptides (CPPs) that were very effective in taking down inflammatory responses induced by several Toll-like receptors
- Uncovered that SLAMF1-derived peptides target both the Triffosome and Myddosome.
- Submitted a PCT patent application for Peptides for Treatment of Sepsis and Cancer (publication number is WO 2021/250212, publication date 16.12.2021)
- Revealed a regulatory role of Mal/TIRAP in TLR8-IRF5-signalling pathway in human phagocytes.
- Demonstrated that TLR2 activation blocks TLR8-signalling at the level of IRF5 phosphorylation.
- Showed that the kinetics of myddosome formation and IRAK-1 modification, as well as the myddosome stability differs in TLR2- versus TLR8 signalling.
- Found that clinical GBS isolates have variable resistance against immune clearance in a blood challenge model.
- Falsified the hypothesis that *LINC01184* or *SLC12A2* have direct regulatory roles for inflammatory or antibacterial responses in human phagocytes or blood ex-vivo.
- Proved the concept that the immune checkpoint inhibitor anti-PD1 can increase TCR/MHC-induced cytokine production in a human blood model.
- Established a method for making gene knock outs in virulent uropathogenic *E. coli* (UPEC) strains using CRISPR/Cas9 technology and made single gene knock mutant of Hemolysine A *(hlyA)*, the cytotoxic necrosis factor 1 *(cnf1)*, Omptin outer membrane protease T *(ompT)*, Toll/interleukin-1 receptor domain-containing protein C *(tcpC)*, that are all verified by genome sequencing.
- Finalized the manuscript "The Rab11-family interacting protein 2 is a regulator of the NLRP3 inflammasome" for publication. Here we have addressed how FIP2 regulates intracellular trafficking of NLRP3 and inflammasome assembly.
- Investigated how bacterial virulence factors such as Hemolysin A and the cytotoxic necrosis factor 1 (CNF1) affect NLRP3 inflammasome activation to cause pyroptotic cell death in human macrophages and THP-1 cells, and how Rab11-FIP2 and phagocytosis is involved.

Ambitions for 2022

- 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 NLRP3 and pro-caspase-1.
- Defining interaction motifs in NLRP3 that binds Rab11-FIP2.
- RNA deep sequencing on Rab11-FIP2 silenced human primary macrophages primed with LPS and treated with Nigericin to activate the NLRP3 inflammasome.
- Investigate how UPEC *DtcpC* and DompT mutants affects NLRP3 inflammasome activation and how Rab11-FIP2 is involved.
- Making a series of double mutants of UPEC double mutants with HlyA and the other above mentioned virulence factors.
- Establish an immune functional blood assay for immunomonitoring of patients, including a flow-cytometry assay for immunophenotyping of leukocytes in whole blood.
- Initiate a clinical study with patients at the intensive care unit and establish a project-specific biobank with treated and non-treated patient blood samples.
- Test SLAMF1-derived peptides in an animal sepsis model and in a myocardial infarction model.

Theme 2:
Molecular Mechanisms of Infection and Inflammation

Theme Manager: Professor Trude Helen Flo



Human primary macrophage infected with *M. avium* (blue) and stained for lysosomes (LAMP1, red) and mitochondria (TOMM20, green). 63x objective followed by iterative deconvolution (Gidon et al., 2021). Photo: Alexandre Gidon

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 2021

In theme 2 we seek to understand infection by studying both the pathogens and the host, from single cells to pre-clinical animal models and in patients. Cell death is an important host defense mechanism and intrinsically linked with inflammation. We have discovered that the splicing factor Raver1 and pre-mRNA splicing regulates cell death, inflammation and host resistance to bacterial infection via RIPK1/caspase-8 signaling. We have further identified other pathways of innate immunity that are also controlled by Raver1. This work will be continued in 2022 along with studies on pore-forming gasdermins during bacterial challenge.

Several new international collaborations have been established in this period: with profs. Steinberg and Goldenberg at the Hospital for SickKids/ Univ Toronto, Canada, on the cell-lytic protein, Ninjurin 1, and with the epidemiology unit at NIH headed by prof. Prevots on host-directed therapeutic strategies for non-tuberculous mycobacterial infections. In August, prof. Flo left for a one-year sabbatical in prof. Kagan's lab at Boston Children's hospital/Harvard Medical School, and young investigator Dragset had a 9-month research stay at Germans Trias i Pujol Research Institute, Barcelona, Spain. She also received funding from Tres Cantos Open Lab Foundation to screen for inhibitors towards a virulence target against *M. tuberculosis* at GlaxoSmithKline, Madrid, Spain.

Several systems-scale studies are ongoing at CEMIR and with collaborators in Mangalore, India and at UMass, USA. We have established a mass-spectrometry based proteomics platform detecting succinylated proteins, which is a novel modification relevant to innate immunity. We performed a systematic study to identify novel micropeptides derived from lncRNA using computational proteogenomics analysis. We have also assembled a comprehensive multiOMICS analysis of SARS-CoV-2 infection in human lung epithelial cells and identified several putative drug targets.

We are establishing multicellular co-culture and organoid models to study cellular crosstalk during infection. Last period we established protocols for making induced pluripotent stem cell (iPSC)-derived macrophages. This year we will make iPSC-derived epithelial cells that will be used to build lung-mimetic models for studying mycobacterial- and viral infections. We have finalized an organoid method and identified how the epigenetic modulator LSD1 is critical in the defense against gut bacterial and helminth infections, by controlling epithelial effector responses. In collaborative work we found that helminth products can oppose host-immune responses by directly targeting the epithelium, and that ILC2-derived acetylcholine is mediating mucosal immunity to helminths. Finally, we helped unraveling the mechanism by which helminth infections in the gut predispose for HSV-2 infection in the genital tract.

In 2021 we performed several studies on genetic risk for sepsis and blood stream infections in HUNT, as well as for infections of the skin, soft tissues, and respiratory tract infections. New studies are planned for 2022 and expanded to include meta-analyses in international consortia, as well as biomarker and disease severity predictor studies in COVID-19 and ICU biobanks established at St. Olavs hospital and internationally.

Major achievements 2021

- Finalized organoid screen identifying epigenetic regulators of intestinal epithelial homeostasis (Ostrop J. et al., *Front Cell Dev Biol*)
- Identified the demethylase LSD1 as an important regulator of gut immunity to infection (Parmar et al., *PLoS Path*)
- Contributed to the discovery that ILC2 produce acetylcholine to mediate type 2 immune responses in lung and gut (Roberts et al., *Sci Immunol*)
- Contributed to the identification of helminth products that directly counteract host immune responses (Drurey et al., *J Exp Med*)
- Contributed to work describing how intestinal helminth infections can predispose for viral infections elsewhere in the body (Chetty et al., *Cell Host & Microbe*)
- Described how auto-/paracrine cytokine signaling drive anti-mycobacterial IRF1-IRG1 activity in human macrophages during *M. avium* infection (Gidon et al., *mBio*)
- Finalized a study showing that pyruvate import to mitochondria elicits mitochondrial ROS, which inhibits the growth of *M. avium* in human primary macrophages (Gidon et al., *bioRxiv*)
- Discovered that glycine is cytoprotective by targeting Ninjurin 1 (Sætra et al., *bioRxiv*)
- Published a review on the role of caspase-8 in inflammation and cell death (Orning and Lien, *J Leuk Biol*)
- Identified CMPK2 as a novel interferon-induced gene that is controlled by IRF3-IFNAR signalling axis (Kim et al., *PLoS ONE*).
- Contributed to a comprehensive signalling map of SARS-CoV-2 infection and Bradykinin signalling (Rex et al., *J Cell Commun Signal*).
- Performed a proteomics-based benchmarking study to optimize the monocyte-to-macrophage differentiation protocol for human macrophage models (Pinto et al., *Front Immunol*).
- Described epidemiological and clinical characteristics of immunocompromised patients infected with *Pneumocystis jirovecii* in a twelve-year retrospective study from Norway (Grønseth et al., *BMC Infect Dis*).
- Investigated the precision of a real-time qPCR strategy to distinguish Pneumocystis pneumonia from colonization in immunosuppressed individuals (Grønseth et al., *Microbiol Spectr*).
- Examined the role of a FER single nucleotide polymorphism in risk of developing and dying from bloodstream infection in the population-based HUNT Study (Rogne et al., *Clin Infect Dis*).
- By GWAS we identified LINC01184/SLC12A2 as a novel susceptibility locus for skin and soft tissue infections (Rogne et al., *J Invest Dermatol*).
- Using a GWAS and Mendelian randomization analysis to identify risk factors for respiratory tract infections (Flatby et al., *Clin Microbiol Infect*).
- Identified an association between thyroid function and the risk of bloodstream infections in the HUNT Study (Thorkildsen et al., *Clin Endocrinol*).
- Identified secreted Wnt antagonists as predictors for disease severity and mortality in scrub typhus (Ueland et al., *PLoS Negl Trop Dis*).
- Established a biobank for COVID-19 and participated in the Host Genetics Initiative for mapping of the human genetic architecture of COVID-19 (*Nature*).
- PhD student Hera Kim graduated from theme 2 in September

Ambitions for 2022

- Publish our work identifying how cytokines drive epithelial effector responses and the discovery of an important epithelial-intrinsic feedback loop.
- Identify a specific role for the extracellular matrix in mediating control of gut infections.
- Further explore lung organoids for discoveries of the role of epithelium in immunity to infection
- Complete and publish the project investigating Raver1 splicing factor and its role in innate immunity
- Complete and publish studies of GSDMD in bacterial evasion mechanisms by Yersinia
- Clarify the roles of Ninj1, caspase-8/1 and RIP kinases in infectious and non-infectious cell death and inflammation
- Decoding the pro-inflammatory role of succinate by profiling the proteome succinylation landscape of innate immune signaling in macrophages.
- Publish the multiOMICS-based temporal molecular network of SARS-CoV-2 infection.
- Elucidate the molecular mechanisms of novel differentially regulated metabolites that we identified in the metabolomics screen.
- Publish the CRISPR/Cas9 screens for identification of novel host factors of HIV and Influenza A
- Identify the targets of the central kinase in innate immune signalling, TBK1, through three different proteomics-centred approach.
- Publish findings that metformin and simvastatin show pre-clinical potential as host-directed therapies to M. avium infection in mice
- Finalize and publish collaborative work on cellular immunity of tuberculosis patients receiving adjunct treatment or therapeutic vaccine (with AM D Riise and K Tonby, Oslo University Hospital)
- Finalize studies of TLR8 ligands as latency-reversal agents for HIV "shock-and-kill" therapy
- Establish iPSC-derived epithelial cells and co-culture infection models with macrophages
- Complete and publish projects on mycobacterial infections of Drosophila melanogaster and on M. tuberculosis virulence targets.
- Explore predictors for disease severity and mortality in the established CUT-Covid biobank in collaboration with international consortia.
- Establish a new biobank for intensive care patients and perform OMIC analyses to identify genetic, peptide and lipid biomarkers for organ failure and sepsis outcome.
- Genome-wide association study and meta-analysis for identifying genetic risk of sepsis.
- Investigate the association between pharmacologic and genetic down-regulation of proprotein convertase subtilisin/kexin type 9 (PCSK9) and survival from sepsis.
- Determine how circulating levels of micronutrients affect the risk of gastrointestinal infections, cellulitis, pneumonia and urinary tract infections.
- Characterize the immune activation profiles in streptococcal necrotizing and non-necrotizing skin and soft tissue infections.
- Apply to the ERC Starting Grant funding scheme (M Dragset)

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 2021

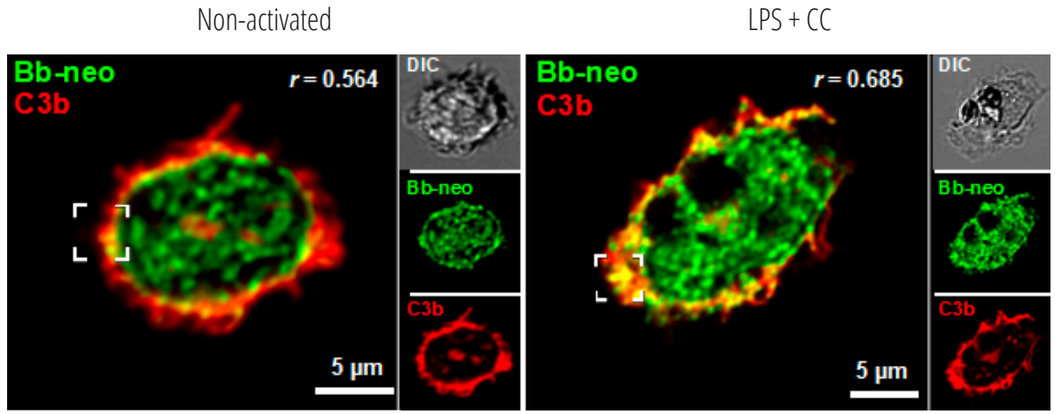
The initial accumulation of oxidized lipids in the vascular cell wall and the resulting cell death are the key events driven by macrophages that define the course of atherogenesis. To get a comprehensive picture of systemwide changes triggered by the uptake of pro-atherogenic molecules we carried out a series of cellular transcriptome profiling experiments and whole genome CRISPR screens. Analysis of the results of these experiments revealed novel connections between cellular metabolism and induction of programmed cell death. We identified novel candidate genes that act as switches that activate either continued accumulation of lipids or trigger cell death. Within the next year we aim to validate our candidates in both immortalized cell lines and primary human cells.

We have shown that CC is a contributing factor in thrombosis by inducing monocyte tissue factor secondary to complement. The atherosclerotic plaques contain toll-like receptor (TLR) activators and thrombosis often occur shortly following infections. Based on this, we show a potentiating effect of CC in diverse TLR-induced coagulation in human whole blood. The combinatory stimulation by CC and LPS potentiates monocyte tissue factor, even at low doses of LPS. Therapeutic intervention is investigated by relevant inhibitors (to C3, C5, CD14, NLRP3 inflammasome). The circulating monocytes could be important mediators of coagulation and interesting targets for treatment of thrombosis.

Cholesterol accumulation, broad PRR activation and vascular malperfusion is shown to be strongly associated to development of placental dysfunction in preeclampsia. This occurs at both sites of the direct maternal-fetal interaction; the uterine wall lining called the decidua and the fetal cell layer covering the placenta. Direct maternal-fetal cellular communication involving inflammatory activation and atherotic lesions have been defined in the uterine wall. The NLRs NLRP3 and NOD1 have been revealed as particularly important players at the maternal-fetal interface in preeclampsia. Metabolomic profiling has identified grades of placental dysfunction. Extensive maternal serum cytokine profiling is used as sensitive measure of normal and deviating maternal immune activation in pregnancy, for causal classification of preeclampsia and novel biomarker selection. 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.

In 2021 we published results from the ASSAIL-study on the effect of the IL-6 receptor-blocker tocilizumab in patients with myocardial infarction (MI). In this study we randomized 101 patients to tocilizumab and 98 patients to placebo. The myocardial salvage index was larger in the tocilizumab group than in the placebo group. Microvascular obstruction was less extensive in the tocilizumab arm. This was the first study to show that tocilizumab increased myocardial salvage in patients with acute STEMI. A large biobank has been collected from this study and several sub-studies exploring the mechanisms of IL-6-blockade in MI are ongoing. We presented data showing that tocilizumab increases citrullinated histone 3 in these patients. Based on the ASSAIL-study, we are planning a multicentre randomized trial with tocilizumab.

CC are found in all stages of atherosclerosis. How our immune system detects CC and how CC cause inflammation is not fully understood. In 2021 we published a paper in Science Immunology describing some of the pieces that were missed in the puzzle. To understand the inflammation in atherosclerosis, we focused on macrophages that are at the intersection of cholesterol homeostasis and inflammation. Our study demonstrates that the intracellular complement system is a key factor in the biological process of the sterile inflammation in atherosclerosis. Our work shows that targeting the intracellular complement could be beneficial in treatment of atherosclerosis.



Intracellular C3/C5 convertase in human monocytes. Confocal microscopy of C3b and Bb-neoepitope of nonactivated (left) and LPS primed and cholesterol crystal activated monocytes. Co-localization of Bb-neo and C3b indicates convertase activity that leads to C5a production (Niyonzima et al., *Sci.Immunol.* 2021).

Major achievements 2021

- 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* 2021)
- Revealed an inflammatory role for NOD1 at the maternal and fetal side of the placenta in preeclampsia (Rakner *et al, Placenta,* 2021)
- Reported sensitive immunological changes throughout normal pregnancy and a strong cytokine boost in post-term pregnancies (Jarmund *et al, Frontiers in Immunology* 2021)
- Defined immunological changes in serum cytokines throughout pregnancy in women with polycystic ovary syndrome (Stokkeland *et al, Journal of Clinical Endocrinology & Metabolism* 2021)
- The inflammatory placenta research by Iversen was interviewed in the national US radio show Science Friday
- Reported effect of tocilizumab on myocardial salvage in MI-patients (*Journal of Am Coll Cardiol* 2021)
- Presented data showing that tocilizumab increases citrullinated histone 3 in MI-patients (*Open Heart* 2021).
- Identified the role of intracellular complement in inflammatory responses that cause atherosclerosis (Niyonzima et al, *Science Immunology*, 2021)

Ambitions for 2022

- Validate specific drivers of macrophage cell death in response to pro-atherogenic signals
- Determine the effects of CC and TLRs in monocyte-induced coagulation and assess effective inhibitory strategies
- Explore the systemic effects of a low-calorie restricted diet on leukocyte PRRs, thromboinflammation, and serum cytokines
- Determine connections between serum cytokines profiles and weight-loss
- Combine 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
- Complete extensive profiling of the maternal immune development throughout pregnancy by measuring serum cytokines in pregnancy complications
- Establish causal classification of subgroups of preeclampsia and fetal growth restriction by metabolomic profiling
- Identify the molecular response to prophylactic aspirin treatment in pregnancy for more targeted selection of high-risk pregnancies benefitting from such treatment
- Expand collection of patient-based biobanks for translational inflammation studies
- Explore cellular effect of tocilizumab using biobanks (monocytes and T-cells) from the ASSAIL-study
- Examine different inflammatory biomarkers and their role in predicting effect of tocilizumab in cardiovascular disease

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

Theme Manager: Professor Arne Sandvik

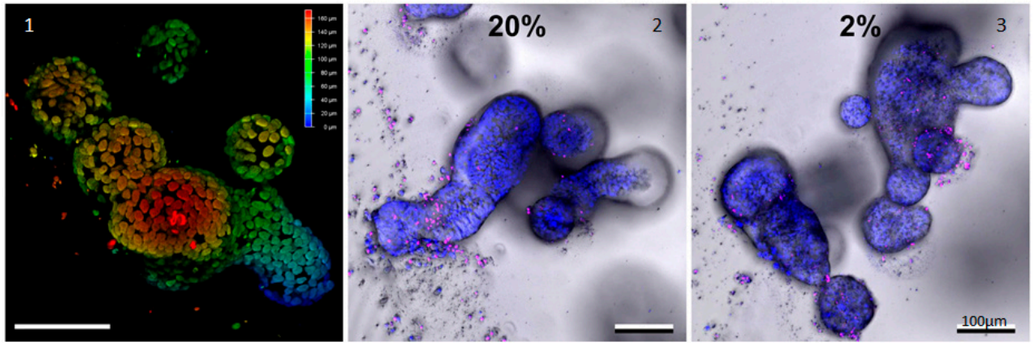
Inflammatory bowel disease (IBD) are chronic diseases arising most likely from an inappropriate inflammatory response to commensal gut microbes. This theme studies the IBD inflammatory process and its consequences at a mechanistic level with hypotheses generated from clinical material. Furthermore, we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

Main activities in 2021

The research group has continued studying colonic epithelial responses to immunological and physiological signals such as cytokines and chemokines. During 2021 work has also encompassed the effect of IBD-approved drugs on inflammation-conditioned organoids to prepare for coming use of organoids as real-life clinical bioassays to circumvent the problem of unpredictable response to disease-modifying drugs. This work is being done in a collection of patient-derived colonoids and in a physiological low-oxygen environment rather than under routine incubator conditions. Simultaneously, our work using mouse in vivo and mouse organoid disease models is used to discover new regulators of intestinal epithelial biology in general, but with specific relevance for inflammatory and infectious diseases. Moreover, efforts to modify colonoids by siRNA and CRISPR-Cas9 techniques are continuing. 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 also ongoing to correlate clinical parameters with laboratory-derived information at the level of the individual patient. This is facilitated e.g. by techniques for generating organoids from biopsies taken from the most informative patients which are 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 □□ 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 2021

- The CAG project to generate highly refined patient data and material from both adults and children is well under way at four different sites.
- A prospective interventional study aimed at predicting treatment response/loss of response, including the role of NGAL as a biomarker, has been wrapped up awaiting analyses.
- Culture conditions for colonoids have been optimized for IBD research, routinely using a 2% oxygen concentration, and drug testing is done applying these parameters.
- Studies on collagenous colitis have identified hallmarks of non-destructive IBD, and further confirmed the utility of NGAL as a biomarker for the disease.
- Studies on the clinically important process of fibrosis in Crohn's disease have highlighted the role of 5-hydroxytryptamine.
- A study about the role of smooth muscle cells in intestinal epithelial repair was published (Martín-Alonso *et al. Nature Communications*)



Detection of morphology and cell death by live imaging of untreated colonoids. Left image shows a 3D depth encoded image of one colonoid at 20% O2, according to the color scale from red (superficial) to blue (deep) on image 1. 2 and 3 show colonoids in 20% or 2% O2 respectively, where NucBlue® Live reagent stains all cell nuclei (blue) and propidium iodide stains dead cell nuclei (red). (Skovdahl et al, 2021.) Photo: Torunn Bruland and Bjørnar Sporsheim.

Ambitions for 2022

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

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

Theme Manager: Professor Therese Standal

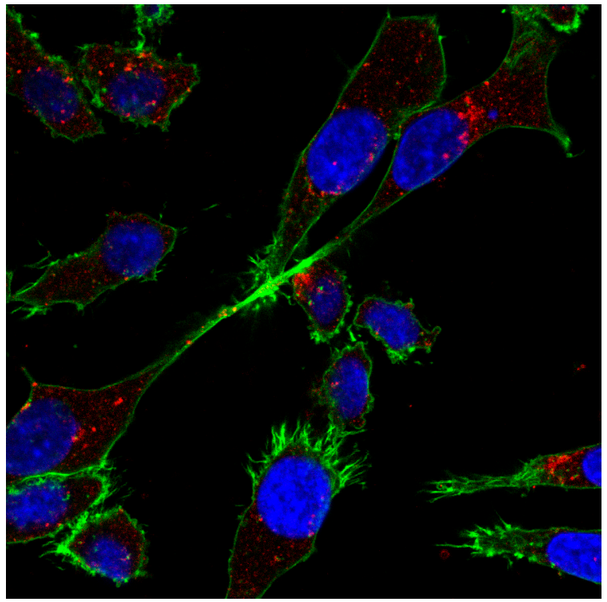
Cancer cells modulate the tumor microenvironment by secreting factors that promote chronic inflammation, inhibit immune surveillance and disrupt bone homeostasis. Pattern-recognition receptors (PRR)s are signalling immune-receptors that mediate inflammatory responses. These receptors sense pathogen or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

Main activities in 2021

Our research focused on regulation and targeting of inflammatory cell death in multiple myeloma, especially through the drug types Smac-mimetics and TAK1-inhibitors. We showed how Smac-mimetics block osteoclastogenesis and thereby could reduce bone damage in multiple myeloma. We also found that TAK1-inhibtors induced cell death in both myeloma cells and osteoclasts. We have continued our work on how immunoglobulins may promote disease progression in multiple myeloma. We have studied interactions between adipocytes and malignant plasma cells in vitro and how obesity may alter disease progression in a pre-clinical myeloma model. A paper on the role of IL-32 for myeloma cell metabolism and survival was accepted for publication.

We have optimized an in vitro model for studying primary human neutrophil polarization and identified markers for activation states in neutrophil polarization states. We also identified differential expression of PRRs in different neutrophils subsets that may be targeted to influence neutrophil polarization states. We have also optimized methods for studying primary human plasmacytoid dendritic cells (pDC)s which are very rare population of innate immune cells in the blood that can trigger potent anti-tumorigenic responses

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



Mulitple myeloma cells stained for IL-32 (red), phalloidin (green) and nucleus (blue).
Photo: Kristin Roseth Aass.

Major achievements in 2021

- A paper on the role of IL-32 for myeloma cell metabolism and survival was accepted for publication (Aass et al. iScience)
- Published a paper on the effect of TAK1-inhibitors in multiple myeloma (Håland et al. Oncotarget 2021.
- Published at paper on the effect of Smac-mimetics on osteoclastogenesis (Moen et al. Cell Death Discovery 2021).
- Identified differential expression of PRRs in different neutrophils subsets
- Optimized methods for studying primary human plasmacytoid dendritic cells (pDC)
- Optimized an in vitro model for studying primary human neutrophil polarization
- Performed RNA sequencing on aggressive cancer cells with constitutive active NRF2 or NRF2 knockdown. Established and performed NRF2 Chip-Seq of the same cells and compiled the gene lists to define NRF2 regulated genes
- Established RNA sequencing of cells sorted from dissociated solid benign and aggressive breast cancers and compared the data with previous lists of RNA isolated from whole tumors and with flow cytometry of immune cell markers in dissociated tumors
- Established and performed MS-MS based quantification of tumor metabolites
- Performed comparisons of immune cell composition of solid tumors made of cancer cells with and without expression of candidate chemokines in an immunocompetent mouse model
- One PhD students defended her thesis

Ambitions for 2022

- Determine the effect of obesity on multiple myeloma disease progression and immune cell function
- Characterize the function of IL-32 in T cells
- Explore the link between infections and IL-32 in multiple myeloma
- Publish new findings on how PRR activation in colon cancer cells induces neutrophil recruitment and polarization.
- Characterize markers of neutrophils polarization states
- Determine how multiple myeloma cells shape neutrophil polarization
- Establish models for obtaining gene editing primary human pDCs in vitro
- Determine how multiple myeloma cells affect pDC differentiation and activation
- Publish how oxidative stress signaling relates to aggressive development of breast cancer and genes driven by constitutive NRF2 signaling in cancer cells
- Publish drivers for different immune cell infiltration of solid tumors and how autophagy in cancer or normal tissue resident cells can be stimulated by certain immune cells
- Further penetrate how autophagy can be regulated through cell-cell interactions and the physiological consequences of such control

Cemir Research Groups

The Inflammation Research Group

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

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

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

The Autophagy and Oxidative Stress Defense Group

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

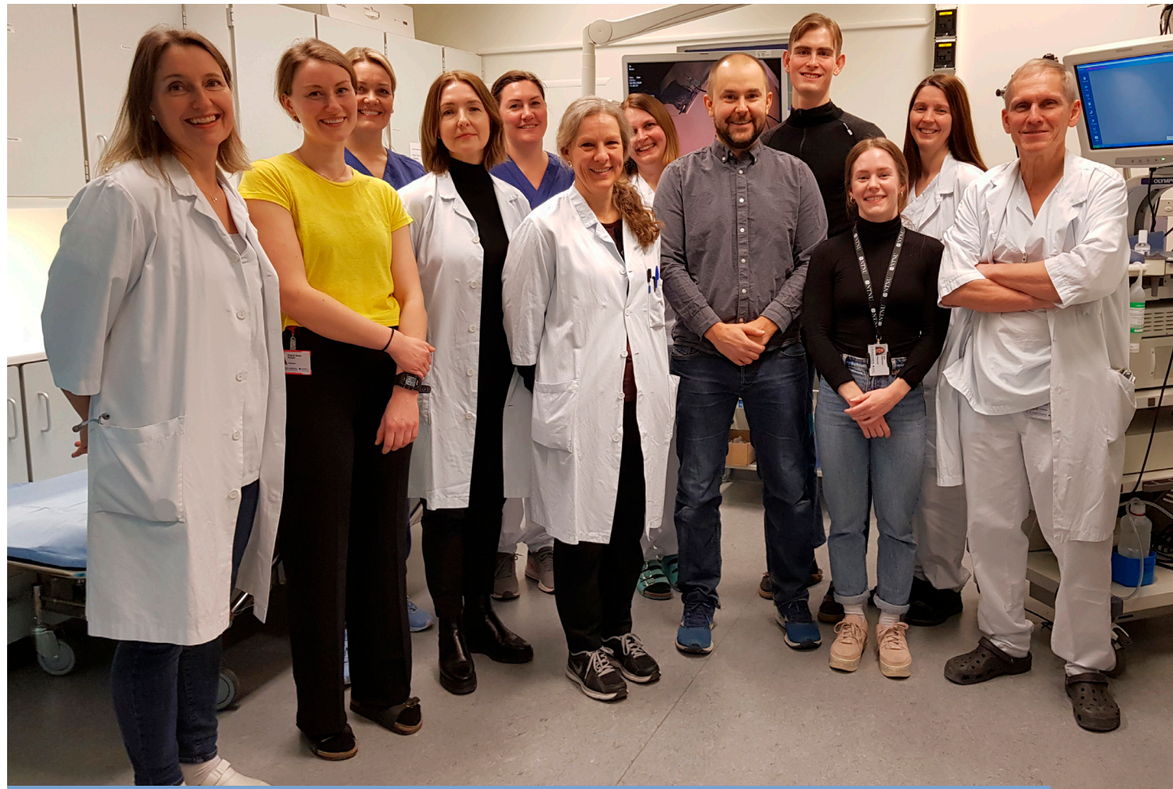
Autophagy is fundamental and strictly controlled mechanism to mobilize amino acids and other nutrients during cellular starvation. Cancer cachexia is a severe, systemic complication characterized by dramatic loss of muscle proteins. We now explore the possibility that some solid tumours secrete compounds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

The Inflammation in Pregnancy Research Group (InPreg)

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

Central collaborators include Professors Line Bjørge at Haukeland University Hospital,Eszter Vanky, Kjell Salvesen and Bård Kulseng at St. Olavs Hospital and Tone Bathen at NTNU. The Research Group is partner in the 12-partner EU 7FP project InterPregGen 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 2021, the group counted 8 persons; Professor Iversen, one post doc, two PhD students, two MD PhD students, one MD student and one Staff Engineer. InPreg published four papers in peer-review journals in 2021, and the research discoveries were publicly disseminated nationally in NRK.no and Gemini, and internationally in the US radio show Science Friday.



The Inflammatory Bowel Diseases (IBD) Group

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

The IBD group is closely connected with clinical medicine, also through combined university/hospital positions, and collaborates with clinicians in 7 different hospitals in the Central Norway health region. The translational aspect 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. This is a multi-site complex biobanking and longitudinal follow-up project enrolling newly diagnosed IBD patients, aiming to produce a finely-granulated set of clinical and biological data for further research on IBD in adults and children.

Work is cross-diciplinary, including cell biologists and molecular biologists in addition to clinicians and gastrointestinal pathologists. 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.

Nationally, the group collaborates mainly with the Arctic University of Norway in Tromsø, and with Oslo University Hospital. The group's international network includes Immunobiology at Yale University (New Haven, USA), Biomedical Sciences at Cedars-Sinai Hospital (Los Angeles, USA), Singapore Immunology Network, Biomedical Sciences Institutes (Singapore), and Institute of Health Research (FISABIO) (Valencia, Spain).

The Bone Microenvironment Group

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

Hypoxic and ER stress and a low grade, chronic inflammation characterize the myeloma bone marrow. Our research is centered on identifying infectious and inflammatory factors present in the bone marrow microenvironment that influence plasma cell survival and cells in the tumor microenvironment. We 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 human-mouse scaffold model allows for a reconstruction of a human hematopoietic environment in scaffolds that are subsequently implanted in immune compromised mice. This model enables engraftment of primary cells from patients. The close collaboration with the clinic combined with the relevant pre-clinical models is key in our search for new treatment targets. 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 had some specific highlights worth mentioning. We published a total of 6 manuscripts, all of which were comprehensive studies and several in journals that are at the scientific level 2. In addition, we are happy that the first two PhD students in our team graduated in 2021. Finally, we are proud that Mara Martín-Alonso was successful in obtaining a 'Young Research Talent' grant from the Research Council of Norway and has started her own team in late 2021.

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

This group started in 2016, is led by Dr. Menno Oudhoff, and in 2021 consisted of 3 Postdocs, 2 PhD students, 1 MSc student, and 1 Research Assistant. We hope 2022 will be another fruitful year with manuscripts and new funding opportunities.

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

Mycobacteria and HIV can cause life-long infections and pose a global health challenge. The COVID-19 pandemic further exemplifies how infectious diseases can paralyze society and cripple the world economy. Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), kills about 1.5 million people each year and the prevalence of non-tuberculous mycobacterial infections caused by *M. avium* is increasing in individuals who are immunocompromised. Mycobacterial infections require long treatment with antibiotics, and drug resistance is emerging. About 35 million people world-wide are infected with HIV and need life-long treatment with anti-viral drugs to survive. And despite the successful invention of vaccines to COVID-19, the pandemic has claimed close to 6 million deaths.

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 investigated 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.

The Research Group is led by Trude H. Flo and includes co-PI Magnus Steigedal, four research scientists, four PhD students, one medical research student and four 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 use these to build lung-mimetic multicellular models for studying cellular crosstalk during infections.

We have strains of Mtb, *M. avium* and *M. smegmatis* available with fluorescence and firefly luciferase, and we have a confocal microscope in our BSL-3 facility for live-cell imaging of Mtb, HIV and SARS-CoV2 infections. Transposon mutant libraries with more than 150 000 mutants in *M. smegmatis, M. avium* and Mtb are available. We also use Focused Ion-Beam Scanning Electron Microscopy at NTNU Nanolab to perform high resolution 3D imaging of infected cells. We collaborate with research groups within CEMIR and with CEMIR affiliated professors E Lien and K Fitzgerald (Univ. Massachusetts, USA), D Underhill (Cedars Sinai) and H Stenmark (Oslo University Hospital (OUS)). Central external collaborators are JC Kagan (Boston Children's hospital, USA), B Steinberg and N Goldenberg (Hospital for SickKids/Univ Toronto, Canada), P Bruheim (NTNU, Dept. Biotechnology), A Simonsen (Univ. Oslo), AM D Riise (OUS), E Rubin (Harvard, USA), N Reiling (Research Center Borstel, Germany), K Prasad (Yenepoya University, India), M Lerm (Linköping University, Sweden).

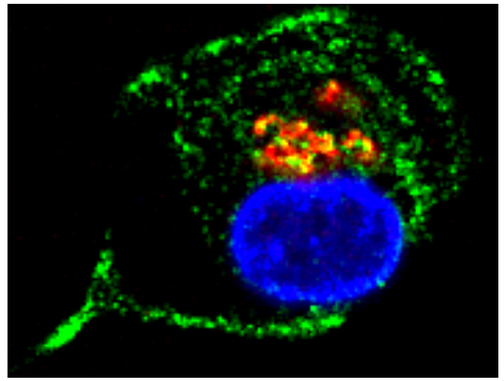
The Systems Inflammation Research Group

Infectious diseases and inflammatory disorders are major contributors to the global burden of disease, thereby having a huge socio-economic impact. Decades of research have unraveled the arsenal of mechanisms by which the host immune system detects an invading microbe and elicit an innate immune response ensuring clearance of the pathogen while exerting a minimal damage to the host. Any failure in this chain could lead to chronic diseases such as Atherosclerosis; as well as devastating conditions like sepsis and sepsis-induced death. It is critical for the host to restore homeostasis and resolve the inflammation upon microbial infections through a collective and meticulous coordination of a number of controlled molecular events such as chromatin remodeling, transcription, translation, post-translational modifications (PTMs) and metabolic reprogramming. The systems inflammation research group aims to specifically study the role of metabolic reprogramming and PTMs (phosphorylation, acetylation and 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.

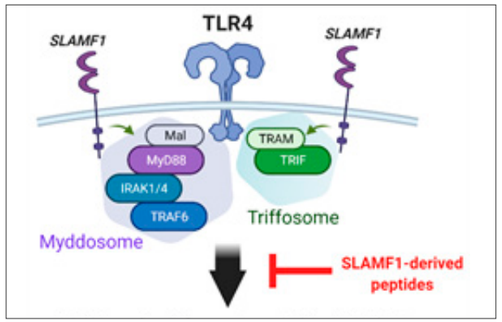
The research group led by Richard K. Kandasamy currently includes 1 Researcher, 1 post-doc and 1 research assistant. We work in close collaboration with CEMIR research groups led by Terje Espevik and Trude H. Flo; as well as Per Bruheim (Department of Biotechnology, NTNU), Denis Kainov (Department of Clinical and Molecular Medicine, NTNU) and Geir Slupphaug (NTNU Proteomics Core). Our international collaborators include Kate Fitzgerald (UMASS Medical School, Worcester, USA), Kate Fitzgerald (UMASS Medical School, Worcester, USA), Egil Lien (UMASS Medical School, Worcester, USA), Giulio Superti-Furga (Center for Molecular Medicine, Vienna, Austria), Christoph Bock (Center for Molecular Medicine, Vienna, Austria), Keshava Prasad (Center for Systems Biology and Molecular Medicine, Yenepoya University, Mangalore, India), Andre Mueller (Center for Molecular Medicine, Vienna, Austria) and Akhilesh Pandey (Mayo Clinic Rochester, USA).

Innovations and Patents

New Drug Candidates with a Potential to Inhibit Inflammatory Responses



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



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

At CEMIR we currently have an innovation project that aims to control harmful inflammation by interfering with the Toll-like receptor (TLR) signaling pathway.

Inflammation plays a crucial role in development and progression of most diseases. Acute or chronic inflammatory states are detrimental for the host health and may lead to severe complications and life-threatening conditions. Among the most prevalent acute inflammatory states is sepsis, which has a very rapid onset and high mortality. Sepsis alone causes 1 in 5 deaths worldwide, killing 11 million people each year, many of them children (WHO global report 2020).

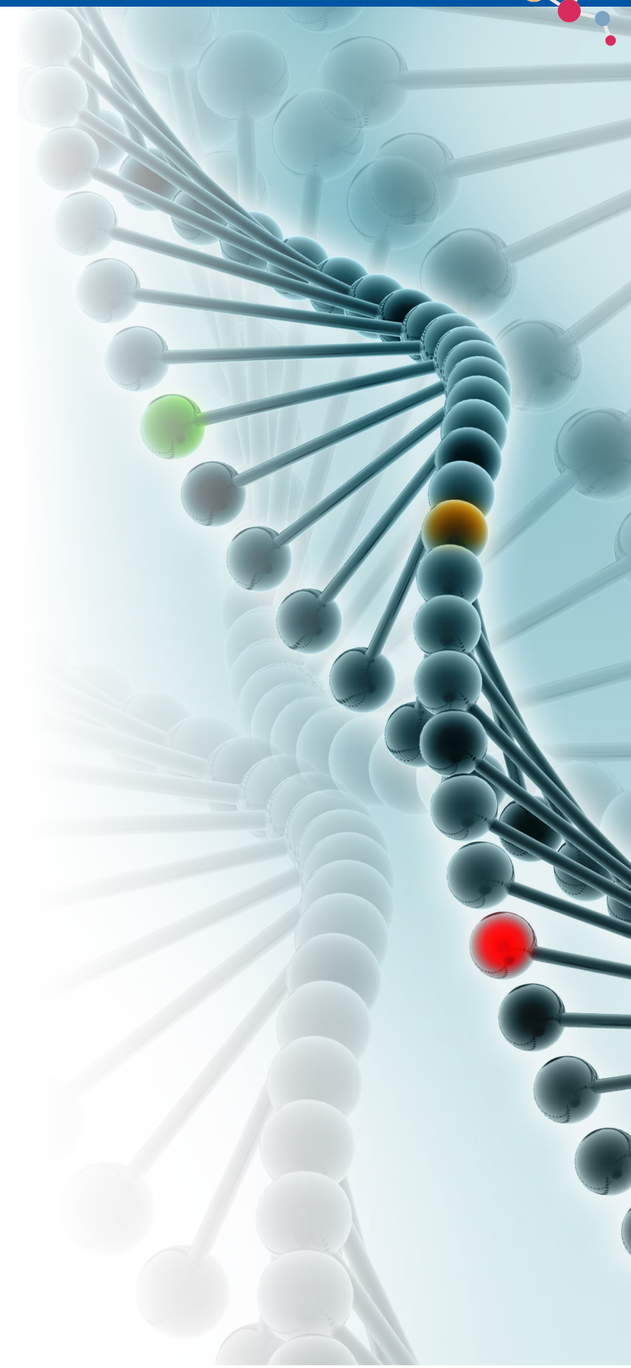
Microbial as well as sterile inflammation is initiated by pattern recognition. This is the initial and most upstream event for the inflammatory response, which subsequently leads to activation of a broad inflammatory network with release of innumerable of mediators. In the presence of a systemic infection, 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.
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:

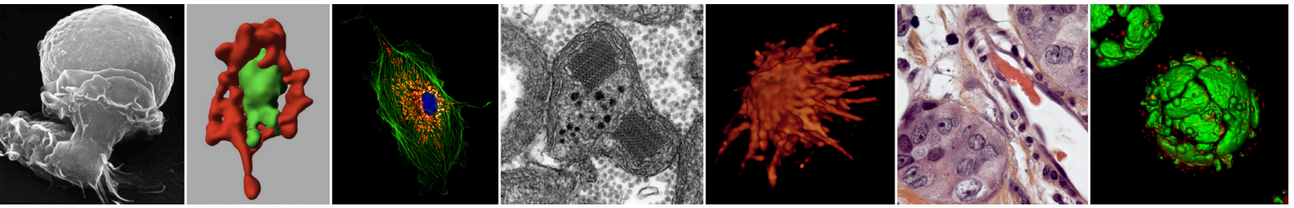
- The effect of peptides is reversible, concentration dependent, with working concentration in 5–20 μM range
- Peptides inhibit pro-inflammatory cytokines (TNFα, Il-1β, IL-6) and IFNβ expression and secretion mediated by TLR4 and TLR9 as well as TLR8-mediated IFNβ expression
- Peptides do not alter TLR2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

The anti-inflammatory peptides and their use are covered by a PCT patent application for Peptides for Treatment of Sepsis and Cancer (publication number is WO 2021/250212, publication date 16.12.2021). Potential applications include acute inflammation like sepsis and myocardial infarction. and chronic inflammation like inflammatory bowel disease.

Given the broad inhibitory activity towards several TLRs and low toxicity, SLAMF1-derived peptides may have high potential for efficient inhibition of pathological inflammation in patients.



Cemir-use of the Imaging Core Facility



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

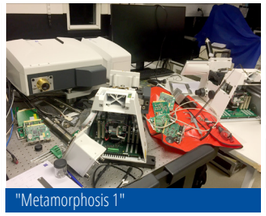
Researchers and students at CEMIR have access to a multitude of different imaging techniques, for live cell studies as well as imaging of fixed cells and tissue preparations. These instruments are all part of the Cellular and Molecular Imaging Core Facility, CMIC, at Faculty of Medicine, NTNU, www.ntnu.edu/mh/cmic.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

In 2019 a Zeiss LSM 880 Airyscan super resolution confocal microscope was installed at CMIC (recently upgraded, se pictures below). During the last years this microscope has become one of the most used imaging system with the majority of users from CEMIR. This microscope uses a special 34 array GaAsP PMT detector to collect more light from the sample for each pixel, resulting in an image with better resolution and greater signal efficiency. In combination with state-of-the-art deconvolution we can achieve resolution down to about 80 nm, which is over two times better than conventional confocal microscopes. The instrument is otherwise well equipped with an incubator system for controlled temperature and CO2 environment.

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

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

"Before"

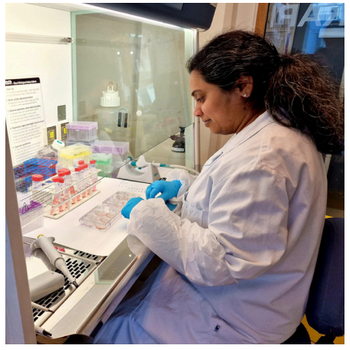


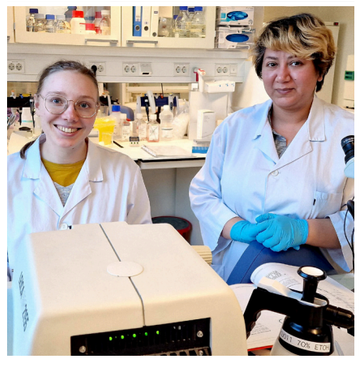
"Metamorphosis 1"

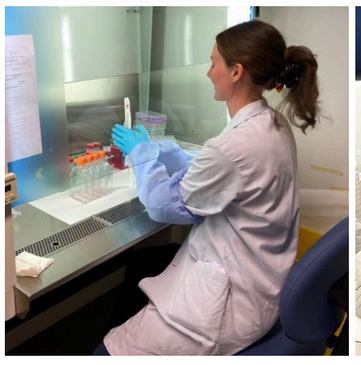
"Metamorphosis 2"

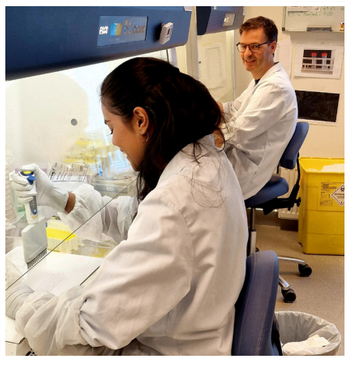
"Finished"

Pictures above: Reconstruction of the Zeiss Airyscan confocal microscope, to increase the imaging possibilities.

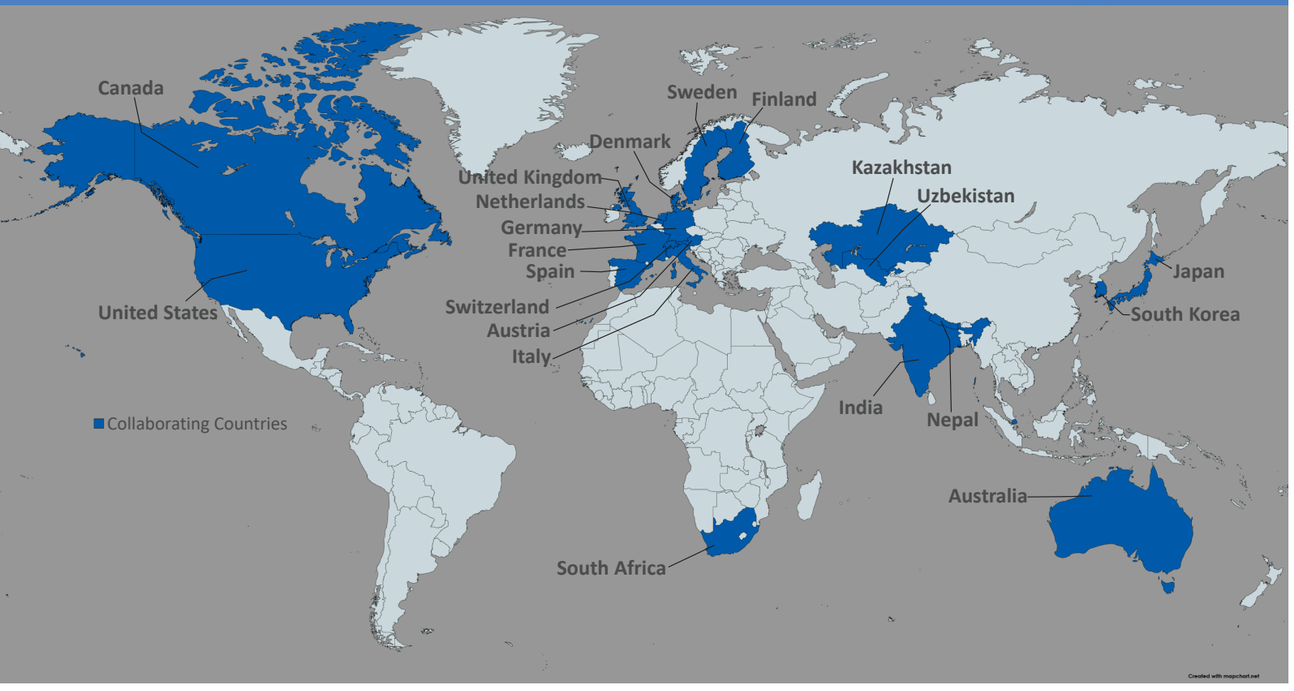








International Collaboration



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

Six outstanding professors from other institutions are affiliated with CEMIR: Kate Fitzgerald and Egil Lien from UMass Boston, David Underhill from Cedars-Sinai LA, Eicke Latz from Univ. Bonn, and Harald Stenmark and Tom Eirik Mollnes from Oslo University Hospital. They work in the fields of cell biology and innate immunity and contribute extensively to the research program at the Centre, as well as hosting and supervising our PhD students and post docs.

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

English is our daily working and teaching language
36 % of the CEMIR staff is international, representing 16 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 2021

Through basic research on molecular innate immune responses our final goal is to develop new therapeutic approaches for inflammatory and infectious diseases. We explore inflammatory pathways in diseases such as atherosclerosis and preeclampsia, multiple myeloma and inflammatory bowel disease (IBD) as well as in several infections such as tuberculosis, sepsis and hiv to develop biomarkers and stratification tools for personalized treatment strategies in these diseases. To achieve this goal in translational medicine, we have established a close collaboration between CEMIR and St. Olav's hospital in several projects. In 2021, we have published results from clinical studies and interventional trials in several of the themes. First, we published the randomized trial of Interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction. In studies of IBD, we identified mucosal and fecal neutrophil gelatinase-associated lipocalin as potential biomarkers for collagenous colitis. Moreover, we established patient derived colonoids as drug testing platforms-critical importance of oxygen concentration. We also investigated the role of intracellular IL-32 in regulating mitochondrial metabolism, proliferation, and differentiation of malignant plasma cells from multiple myeloma patients. In all these projects a close collaboration between basic researchers and clinicians was established. An important arena for this close interaction with St Olav `s hospital is the two clinical academic groups (CAG) that have budded out from CEMIR. CAGs, which consist of researchers and clinicians from the NTNU and St Olav's hospital, as well as other hospitals in the health region, have clearly been strengthening clinical studies of IBD and multiple myeloma. Similarly, the establishment of the Colorectal Cancer (CRC) Research enhance the interactions between researchers at CEMIR and gastrosurgeons and oncologists at St Olav's hospital. Several of the projects at CEMIR also include studies from clinical biobanks. In preclampsia, using these biobanks, we have presented cytokine patterns in maternal serum from first trimester to term and beyond in normal pregnancies, as well as throughout pregnancy in women with polycystic ovary syndrome. Also, by using biopsies, we have characterized both the role of decidua and placenta in normal pregnancies and preeclampsia. Finally, for many of our projects in infectious diseases, we have linked clinical and genetic data from the large genotyped HUNT2 study with clinical registries such as the Mid-Norway Sepsis Registry.

Completed PhDs in 2021 for the degree of Philosophiae Doctor

Rosalie Theda Margien Zwiggelaar
defended her thesis "Epigenetic control of the intestinal epithelium - A role for lysine-specific demethylase 1A during homeostasis and disease" April 29., 2021.
Researcher Menno Oudhoff and Professor Trude Helen Flo has been her supervisors.

Håvard Takle Lindholm
defended his thesis "Defining changes in the intestinal epithelium in early life and in response to infections" June 22., 2021.
His supervisors have been researcher Menno Oudhoff and Professor Finn Drabløs.

Hera Kim
defended her thesis "Decoding the Metabolic Reprogramming Underlying Toll-like Receptor Signaling"
September 14., 2021.
Associate professor Richard Kumaran Kandasamy and professor Per Bruheim has been her supervisors.

Ingrid Nyhus Moen
defended her thesis "Pharmaceutical targeting of RIPK1-signaling: Characterization of cell death in human macrophage systems and therapeutic potential in multiple myeloma"
December 1st, 2021.
Researcher Kristian K. Starheim and Professor Geir Bjørkøy have been her supervisors.

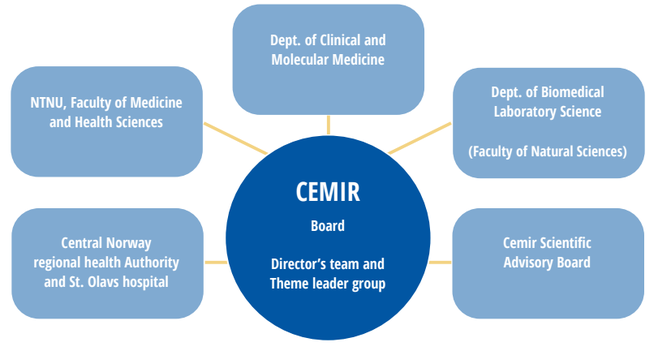
About Cemir

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

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

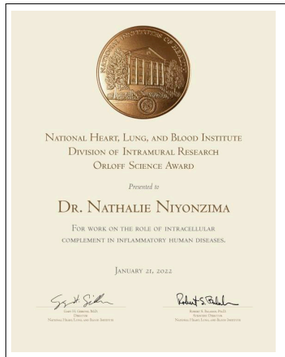
CEMIR board
One board meeting was held in 2021.
From 2021 the board members are:
- Torstein Baade Rø – (Board chairman) Vice Dean, Faculty of Medicine and Health Sciences, NTNU
- Magnus Steigedal – Head of Dep. of Clinical and Molecular Medicine, NTNU
- Pål Romundstad – Vice Dean, Faculty of Medicine 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

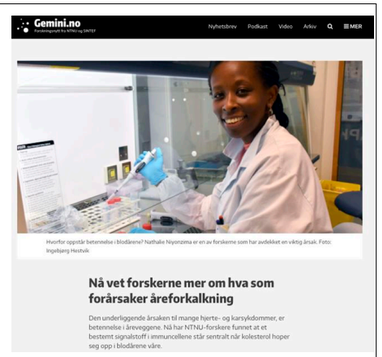


CEMIR Scientific Advisory Board (SAB)
The SAB members are:
- Professor Douglas Golenbock, University of Massachusetts Medical School
- Professor Alan Aderem, Seattle Biomedical Research Institute
- Professor Göran Hansson, Karolinska Institutet
- Professor Stefanie Vogel, University of Maryland medical Center
- Professor Lynda Stuart, B & M Gates Foundation

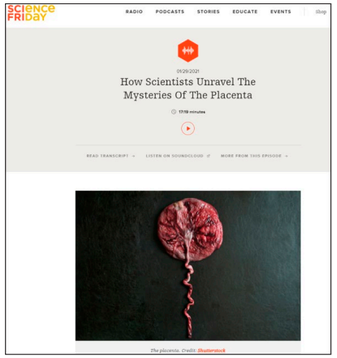
The function of SAB is to review the scientific progress of the Centre and to give guidance to future research directions.

Science Communication and Outreach Activity





Nathalie Niyonzima and colleagues have revealed an important contributor to inflammation in atherosclerosis. For this work, she and others at the Kemper lab (current and former members) received the «NHBL Orloff Science Award», which emphasizes the teamwork within the Division of Intramural Research at NHI.



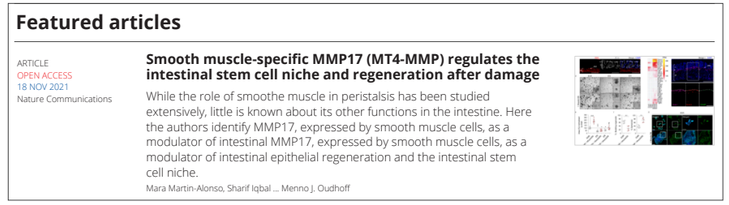
Ann-Charlotte Iversen was invited to talk about the InPreg group's research and latest findings of cholesterol crystals in the placenta in the US radio show Science Friday January 2021. Their research was also described in Gemini.

An image from the work of Naveen Parmar and coworkers was selected for the cover of the March edition of Science Immunology.

A collaboration paper between people at Menno Oudhoff'sgroup and researchers in Cape Town that was published in Cell Host & Microbereceived a lot of publicity.

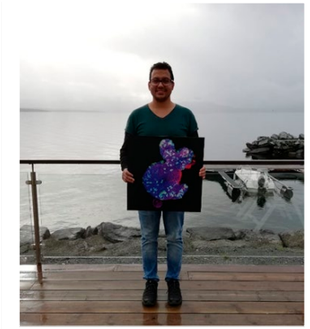
The work by Anders Jarmund, Live Stokkeland and coworkers received positive attention in media, with articles in both Gemini and NRK.

The work by Mara Martín-Alonso and coworkers published in Nature Communications was selected forthe Editors' Highlights pages to showcase the best papers recently published the stem cell area.



Bjørnar Sporsheim and CMIC helped making an educational film for high school students with a focus on imaging in cell and molecular biology.

Jan Kristian Damås talked about the Covid-19 situation at a "Fredags-forelesning" January 2021.



Naveen Parmar received a prize for his confocal picture of a mouse organoid at the 5th conference of Digital Life Norway Research School that was held in Tromsø.

Ragnhild Sofie Ragnhildstveit Sætra won the prize for best oral presentation at the IBA Annual Meeting November 2021, with the talk «Molecular mechanisms in Mycobacterium tuberculosis-infected macrophage".

Guest Lectures in 2021

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 electronically.

Professor Stefan Kaufmann,
Director Emeritus at the Max Planck Institute for Biophysical Chemistry, Göttingen, Professor of Microbiology and Immunology at Charité University Clinics Berlin, and former Director of the Department of Immunology at Max Planck Institute for Infection Biology, Berlin.
Guest lecture May 5th: *VPM1002, the most advanced live vaccine candidate against tuberculosis.*

Professor Egil Lien,
University of Massachusetts Medical School, USA, and affiliated professor at CEMIR.
Guest lecture November 8th: Regulation of cytotoxicity and inflammation mediated by RIPK1-caspase-8.

Professor Harald Stenmark,
University of Oslo and affiliated professor at CEMIR. Guest lectures:
April 6th: *Sealing holes in cellular membranes.*
November 8th: *Macropinocytosis in nutrient acquisition and bacterial uptake.*

Profesor Eicke Latz,
University of Bonn and affiliated professor at CEMIR.
Guest lecture October 25th: *Mitochondrial damage is recognized by a novel inflammasome.*

Professor David Underhill,
Cedars-Sinai, Los Angeles, USA, and affiliated professor at CEMIR.
Guest lecture October 28th: *The Mycobiome and Cancer Therapy.*

Cemir Staff 2021

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 2021, 66 scientific staff members, 14 technicians, 13 students and one administrative coordinator were associated with the Centre.

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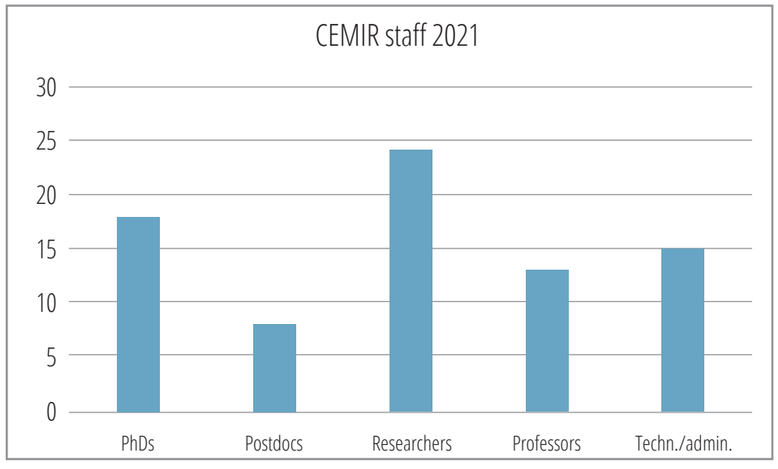


Name		Position	Nationality	Research group
Aass	Kristin Roseth	Postdoctor	Norway	Bone disease
Alonso	Mara	Researcher	Spain	Regeneration
Andersen	Sonja	Staff engineer	Norway	Support group
Bjørkøy	Geir	Professor	Norway	Autophagy
Bokil	Ansooya	PhD	India	Autophagy
Boyartchuk	Victor	Researcher	Ucraine	Inflammation
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
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
Kandasamy	Richard Kumaran	Associate professor	India	Systems inflammation
Kastnes	Martin	PhD	Norway	Bone disease
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	
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
Mestvedt	Ingvild Bergdal	Researcher	Norway	Inflammation
Meås	Hany Zakaria	Postdoctor	Egypt	MYCOVIR
Moen	Siv	Researcher	Norway	Bone disease
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
Oudhoff	Menno	Researcher	Netherlands	Regeneration
Parmar	Naveen	Postdoctor	India	Regeneration
Pettersen	Kristine	Postdoctor	Norway	Autophagy
Pinto	Sneha Maria	Postdoctor	India	Systems inflammation
Rad	Leila Heidary	Staff engineer	Iran	Regeneration
Ragunathan	Kalaiyarasi	PhD	Sri Lanka	Inflammation
Rakner	Johanne Johnsen	PhD	Norway	InPreg
Rasheed	Kashif	Postdoctor	Pakistan	Inflammation
Rokstad	Anne Mari	Researcher	Norway	Inflammation
Roseth	Ingrid Aass	PhD	Norway	Bone diease
Ryan	Liv	Staff engineer	Norway	Support group
Sandvik	Arne	Professor	Norway	IBD
Seljeseth	Emilie	Researcher	Norway	Inflammation
Selvik	Linn-Karina	Staff engineer	Norway	Support group
Serra	Ignacio Catalan	Postdoctor	Spain	IBD
Sivakumar	Niruja	PhD	Norway	MYCOVIR
Spanjers	Roos	Staff engineer	Netherlands	Regeneration
Sporsheim	Bjørnar	Staff engineer	Norway	Support group
Standal	Therese	Professor	Norway	Bone disease
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	InPreg
Subbannayya	Yashwanth	Researcher	India	Systems inflammation
Sundan	Anders	Professor	Norway	
Sætra	Ragnhild	PhD	Norway	MYCOVIR
Tryggestad	Synne	PhD	Norway	Bone disease
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
Ødegaard	Julia	Anne Mari	Norway	Forkser
Yao	Rouan	PhD	USA	Regeneration

Cemir Scientific Publications 2021

Aass, Kristin Roseth; Mjelle, Robin; Kastnes, Martin Haugrud; Tryggestad, Synne Stokke; van den Brink, Luca Mare; Roseth, Ingrid Aass; Westhrin, Marita; Zahoor, Muhammad; Moen, Siv Helen; Nedal, Tonje Marie Vikene; Buene, Glenn; Misund, Kristine; Sponaas, Anne-Marit; Ma, Qianli; Sundan, Anders; Groen, Richard WJ; Slørdahl, Tobias Schmidt; Waage, Anders; Standal, Therese.
Intracellular IL-32 regulates mitochondrial metabolism, proliferation, and differentiation of malignant plasma cells. iScience 2021 ;Volum 25.(1)
UiO NTNU STO

Alme, Katinka Nordheim; Askim, Torunn; Assmus, Jörg; Mollnes, Tom Eirik; Naik, Mala; Næss, Halvor; Saltvedt, Ingvild; Ueland, Per- Magne; Ulvik, Arve; Knapskog, Anne-Brita.
Investigating novel biomarkers of immune activation and modulation in the context of sedentary behaviour: a multicentre prospective ischemic stroke cohort study. BMC Neurology 2021 ;Volum 21.(1) s.1-9
UiB HVprivate NTNU OUS NLSH SUS STO HAUKELAND UiO UiT

Alme, Katinka Nordheim; Ulvik, Arve; Askim, Torunn; Assmus, Jörg; Mollnes, Tom Eirik; Naik, Mala; Næss, Halvor; Saltvedt, Ingvild; Ueland, Per Magne; Knapskog, Anne Brita.
Neopterin and kynurenic acid as predictors of stroke recurrence and mortality: a multicentre prospective cohort study on biomarkers of inflammation measured three months after ischemic stroke. BMC Neurology 2021 ;Volum 21.(1) s.1-11
UiB HVprivate NTNU HAUKELAND UiO UiT NLSH OUS SUS STO

Alonso, Mara Martin; Iqbal, Sharif; Vornewald, Pia; Lindholm, Håvard Takle; Damen, Mirjam J.; Martínez, Fernando; Hoel, Sigrid; Sanchez, Alberto Diez; Altelaar, Maarten; Katajisto, Pekka; Arroyo, Alicia G.; Oudhoff, Menno.
Smooth muscle-specific MMP17 (MT4-MMP) regulates the intestinal stem cell niche and regeneration after damage. Nature Communications 2021 ;Volum 12.(1)
NTNU

Askarian, Fatemeh; Uchiyama, Satoshi; Masson, Helen; Sørensen, Henrik Vinther; Golten, Ole; Bunæs, Anne Cathrine; Mekasha, Sophanit; Kjendseth, Åsmund Røhr; Kommedal, Eirik Garpestad; Ludviksen, Judith K; Arntzen, Magnus Øverlie; Schmidt, Benjamin; Zurich, Raymond H.; Van Sorge, Nina M.; Eijsink, Vincent G.H.; Krengel, Ute; Mollnes, Tom Eirik; Lewis, Nathan E.; Nizet, Victor; Vaaje- Kolstad, Gustav.
The lytic polysaccharide monooxygenase CbpD promotes Pseudomonas aeruginosa virulence in systemic infection. Nature Communications 2021 ;Volum 12. s.1-19
UiO NTNU OUS NLSH NMBU UiT

Bakke, Ingunn; Walaas, Gunnar Andreas; Bruland, Torunn; Røyset, Elin Synnøve; Granlund, Atle van Beelen; Escudero-Hernandez, Celia; Thorsvik, Silje; Münch, Andreas; Sandvik, Arne Kristian; Østvik, Ann Elisabet.
Mucosal and faecal neutrophil gelatinase-associated lipocalin as potential biomarkers for collagenous colitis. Journal of gastroenterology 2021 ;Volum 56. s.914-927 NTNU STO

Bjorkli, Christiana; Louet, Claire; Flo, Trude Helen; Hemler, Mary Elizabeth; Sandvig, Axel; Sandvig, Ioanna.
In Vivo Microdialysis in Mice Captures Changes in Alzheimer´s Disease Cerebrospinal Fluid Biomarkers Consistent with Developing Pathology.
Journal of Alzheimer's Disease 2021 ;Volum 84.(4) s.1781-1794
STO NTNU

Braga, Tarcio Teodoro; Davanso, Mariana Rodrigues; Mendes, Davi; de Souza, Tiago Antonio; de Brito, Anderson Fernandes; Cruz, Mario Costa; Hiyane, Meire Ioshie; de Lima, Dhemerson Souza; Nunes, Vinicius; de Fátima Giarola, Juliana; Souto, Denio Emanuel Pires; Próchnicki, Tomasz; Lauterbach, Mario A.R.; Biscaia, Stellee Marcela Petris; de Freitas, Rilton Alves; Curi, Rui; Pontillo, Alessandra; Latz, Eicke; Camara, Niels Olsen Saraiva.
Sensing soluble uric acid by Naip1-Nlrp3 platform. Cell Death & Disease 2021 ;Volum 12.(2)
NTNU

Broch, Kaspar; Anstensrud, Anne Kristine; Woxholt, Sindre; Sharma, Kapil Kishore; Tøllefsen, Ingvild Maria; Bendz, Bjørn; Aakhus, Svend; Ueland, Thor; Amundsen, Brage H.; Damås, Jan Kristian; Berg, Erlend; Bjørkelund, Elisabeth; Bendz, Christina; Hopp, Einar; Kleveland, Ola; Stensæth, Knut Haakon; Opdahl, Anders; Kløw, Nils-Einar; Seljeflot, Ingebjørg; Andersen, Geir Øystein; Wiseth, Rune; Aukrust, Pål; Gullestad, Lars.
Randomized Trial of Interleukin-6 Receptor Inhibition in Patients With Acute ST-Segment Elevation Myocardial Infarction. Journal of the American College of Cardiology 2021 ;Volum 77.(15) s.1845-1855
OUS UiO NTNU STO UiT

Bruland, Torunn; Østvik, Ann Elisabet; Sandvik, Arne Kristian; Hansen, Marianne Dore.
Host-Viral Interactions in the Pathogenesis of Ulcerative Colitis. International Journal of Molecular Sciences 2021 ;Volum 22.(19)
STO NTNU

Catalan-Serra, Ignacio.
Young GI angle: Working abroad with the family: Mission impossible?. United European Gastroenterology journal 2021 ;Volum 9.(8) s.982-983
HNT NTNU

Chaban, Viktoriia; Nakstad, Espen R.; Stær-Jensen, Henrik; Schjalm, Camilla; Seljeflot, Ingebjørg; Vaage, Ingvar Jarle; Lundqvist, Christofer; Saltyte Benth, Jurate; Sunde, Kjetil; Mollnes, Tom Eirik; Andersen, Geir Øystein; Pischke, Soeren.
Complement activation is associated with poor outcome after out-of-hospital cardiac arrest. Resuscitation 2021 ;Volum 166. s.129-136
NLSH UiO OUS AHUS UiT NTNU

Coelho Medeiros, Pedro Miguel; Schjalm, Camilla; Christiansen, Dorte; Sokolova, Marina; Pischke, Soeren Erik; Würzner, Reinhard; Mollnes, Tom Eirik; Barratt-Due, Andreas.
Vitamin C, Hydrocortisone, and the Combination Thereof Significantly Inhibited Two of Nine Inflammatory Markers Induced by Escherichia Coli But Not by Staphylococcus Aureus - When Incubated in Human Whole Blood. Shock 2021 ;Volum 57.(1) s.72-80
NTNU UiT NLSH OUS UiO

Coron, Abba E.; Kjesbu, Joachim Sebastian; Kjærnsmo, Fredrikke; Oberholzer, José; Rokstad, Anne Mari A.; Strand, Berit Løkensgard.
Pericapsular fibrotic overgrowth mitigated in immunocompetent mice through microbead formulations based on sulfated or intermediate G alginates. Acta Biomaterialia 2021 ;Volum 137. s.172-185
NTNU STO

Debler, Lisa; Palmer, Annette; Braumüller, Sonja; Klohs, Bettina; Mollnes, Tom Eirik; Holzmann, Karlheinz; Huber-Lang, Markus; Halbgebauer, Rebecca.
Hemorrhagic shock induces a rapid transcriptomic shift of the immune balance in leukocytes after experimental multiple injury. Mediators of Inflammation 2021 ;Volum 2021:6654318. s.1-9
UiO UiT NTNU NLSH OUS

Di Fiore, Riccardo; Suleiman, Sherif; Drago-Ferrante, Rosa; Félix, Ana; O'Toole, Sharon A.; O'Leary, John J.; Ward, Mark P.; Beirne, James; Yordanov, Angel; Vasileva-Slaveva, Mariela; Subbannayya, Yashwanth; Pentimalli, Francesca; Giordano, Antonio; Calleja- Agius, Jean.
LncRNA MORT (ZNF667-AS1) in Cancer—Is There a Possible Role in Gynecological Malignancies?. International Journal of Molecular Sciences 2021 ;Volum 22.(15)
NTNU

Escudero-Hernandez, Celia; van Beelen Granlund, Atle; Bruland, Torunn; Sandvik, Arne Kristian; Koch, Stefan; Østvik, Ann Elisabet; Münch, Andreas.
Transcriptomic Profiling of Collagenous Colitis Identifies Hallmarks of Nondestructive Inflammatory Bowel Disease. Cellular and Molecular Gastroenterology and Hepatology (CMGH) 2021 ;Volum 12.(2) s.665-687
NTNU STO

Fevang, Børre; Wyller, Vegard Bruun Bratholm; Mollnes, Tom Eirik; Pedersen, Maria; Asprusten, Tarjei Tørre; Michelsen, Annika Elisabet; Ueland, Thor; Otterdal, Kari.
Lasting Immunological Imprint of Primary Epstein-Barr Virus Infection With Associations to Chronic Low-Grade Inflammation and Fatigue.
Frontiers in Immunology 2021 ;Volum 12.
OUS UiO AHUS UiT NTNU NLSH

Flatby, Helene Marie; Rasheed, Humaira; Ravi, Anuradha; Thomas, Laurent; Liyanarachi, Kristin Vardheim; Afset, Jan Egil; DeWan, Andrew; Brumpton, Ben Michael; Hveem, Kristian; Åsvold, Bjørn Olav; Simonsen, Gunnar Skov; Furberg, Anne-Sofie; Damås, Jan Kristian; Solligård, Erik; Rogne, Tormod.
Risk of lower respiratory tract infections: a genome-wide association study with Mendelian randomization analysis in three independent European populations. Clinical Microbiology and Infection (CMI) 2021
HIM UiT NTNU NMBU UNN STO

Garred, Peter; Tenner, A. J.; Mollnes, Tom Eirik.
Therapeutic Targeting of the Complement System: From Rare Diseases to Pandemics. Pharmacological Reviews 2021 ;Volum 73.(2) s.792-827
OUS NLSH NTNU UiT UiO

Grenne, Bjørnar; Dalen, Håvard; Nordhaug, Dag Ole; Aas, Torgeir Sand; Holte, Espen; Damås, Jan Kristian; Mjølstad, Ole Christian.
Corynebacterium freneyi as a cause of early prosthetic valve endocarditis. BMJ Case Reports 2021 ;Volum 14:e245152.(11) s.1-5
HMR STO NTNU HNT

Grønseth, Stine; Rogne, Tormod; Hannula, Raisa; Åsvold, Bjørn Olav; Afset, Jan Egil; Damås, Jan Kristian.
Epidemiological and clinical characteristics of immunocompromised patients infected with Pneumocystis jirovecii in a twelve-year retrospective study from Norway. BMC Infectious Diseases 2021 ;Volum 21.(1)
NTNU STO

Grønseth, Stine; Rogne, Tormod; Hannula, Raisa; Åsvold, Bjørn Olav; Afset, Jan Egil; Damås, Jan Kristian.
Semiquantitative Real-Time PCR to Distinguish Pneumocystis Pneumonia from Colonization in a Heterogeneous Population of HIV-Negative Immunocompromised Patients. Microbiology spectrum 2021 ;Volum 9.(1) s.e0002621
NTNU STO

Helseth, Ragnhild; Kleveland, Ola; Ueland, Thor; Wiseth, Rune; Damås, Jan Kristian; Broch, Kaspar; Michelsen, Annika Elisabet; Bendz, Bjørn; Gullestad, Lars; Aukrust, Pål; Seljeflot, Ingebjørg.
Tocilizumab increases citrullinated histone 3 in non-ST segment elevation myocardial infarction. Open heart 2021 ;Volum 8.(1)
OUS STO UiO NTNU UiT

Hepowit, Nathaniel L.; Kolbe, Carl-Christian; Zelle, Sarah R.; Latz, Eicke; MacGurn, Jason A..
Regulation of ubiquitin and ubiquitin-like modifiers by phosphorylation.
The FEBS Journal 2021
NTNU

Holt, Margrethe Flesvig; Michelsen, Annika Elisabet; Shahini, Negar; Bjørkelund, Elisabeth; Bendz, Christina; Massey, Richard J; Schjalm, Camilla; Halvorsen, Bente; Broch, Kaspar; Ueland, Thor; Gullestad, Lars; Nilsson, Per; Aukrust, Pål; Mollnes, Tom Eirik; Louwe, Maria Cornelia.
The Alternative Complement Pathway Is Activated Without a Corresponding Terminal Pathway Activation in Patients With Heart Failure. Frontiers in Immunology 2021 ;Volum 12.
OUS UiO UiT NLSH NTNU

Håland, Erling; Moen, Ingrid Nyhus; Veidal, Elias; Hella, Hanne; Misund, Kristine; Slørdahl, Tobias Schmidt; Starheim, Kristian K..
TAK1-inhibitors are cytotoxic for multiple myeloma cells alone and in combination with melphalan. OncoTarget 2021 ;Volum 12.(21) s.2158-2168
NTNU STO

Islam, Rakibul; Islam, Mohammad Mirazul; Nilsson, Per H.; Mohlin, Camilla; Hagen, Kjersti Thorvaldsen; Paschalis, Eleftherios I.; Woods, Russell L.; Bhowmick, Sabuj Chandra; Dohlman, Claes H.; Espevik, Terje; Chodosh, James; Gonzalez-Andrades, Miguel; Mollnes, Tom Eirik.
Combined blockade of complement C5 and TLR co-receptor CD14 synergistically inhibits pig-to-human corneal xenograft induced innate inflammatory responses. Acta Biomaterialia 2021 ;Volum 127. s.169-179
UiO OUS NTNU UiT NLSH

Jarmund, Anders Hagen; Giskeødegård, Guro F.; Rakner, Johanne Johnsen; Stokkeland, Live Marie; Ryssdal, Mariell; Steinkjer, Bjørg; Løvvik, Tone Shetelig; Stafne, Signe Nilssen; Bjørge, Line; Vanky, Eszter; Iversen, Ann-Charlotte.
Systemic immunological perturbations and placental pathology in preeclampsia. Placenta 2021 ;Volum 112. s.e18-e19
NTNU UiB

Jarmund, Anders Hagen; Giskeødegård, Guro F.; Rakner, Johanne Johnsen; Stokkeland, Live Marie; Ryssdal, Mariell; Steinkjer, Bjørg; Løvvik, Tone Shetelig; Stafne, Signe Nilssen; Vanky, Eszter; Iversen, Ann-Charlotte.
Longitudinal serum cytokine profiles in gestational hypertension and preeclampsia. Pregnancy Hypertension 2021 ;Volum 25. Suppl. 1. s.e18-e18
NTNU

Jarmund, Anders Hagen; Giskeødegård, Guro F.; Ryssdal, Mariell; Steinkjer, Bjørg; Stokkeland, Live Marie; Madssen, Torfinn Støve; Stafne, Signe Nilssen; Stridsklev, Solhild; Moholdt, Trine; Heimstad, Runa Kristine; Iversen, Ann-Charlotte; Vanky, Eszter.
Markante immunologiske forandringer i ulike stadier av svangerskapet. Gynekologen 2021 (3) s.43-43
NTNU

Jarmund, Anders Hagen; Giskeødegård, Guro F.; Ryssdal, Mariell; Steinkjer, Bjørg; Stokkeland, Live Marie; Madssen, Torfinn Støve; Stafne, Signe Nilssen; Stridsklev, Solhild; Moholdt, Trine; Heimstad, Runa Kristine; Vanky, Eszter; Iversen, Ann-Charlotte.
Cytokine Patterns in Maternal Serum From First Trimester to Term and Beyond. Frontiers in Immunology 2021 ;Volum 12. s.1-15 NTNU STO

Kim, Hera; Subbannayya, Yashwanth; Humphries, Fiachra; Skjesol, Astrid; Pinto, Sneha M.; Giambelluca, Miriam; Espevik, Terje; Fitzgerald, Katherine A.; Kandasamy, Richard Kumaran.
UMP-CMP kinase 2 gene expression in macrophages is dependent on the IRF3-IFNAR signaling axis. PLOS ONE 2021 ;Volum 16.(10) s.1-24
NTNU

Langeland, Halvor Johannes Breivik; Damås, Jan Kristian; Mollnes, Tom Eirik; Ludviksen, Judith K; Ueland, Thor; Michelsen, Annika Elisabet; Løberg, Magnus; Bergum, Daniel; Nordseth, Trond; Skjærvold, Nils Kristian; Klepstad, Pål.
The inflammatory response is related to circulatory failure after out-of-hospital cardiac arrest: A prospective cohort study. Resuscitation 2021 ;Volum 170. s.115-125
NLSH HMR OUS NTNU UiT UiO STO

Laustsen, Anders; van der Sluis, Renée M.; Gris-Oliver, Albert; Hernández, Sabina Sánchez; Cemalovic, Ena; Tang, Hai Q.; Pedersen, Lars Henning; Uldbjerg, Niels; Jakobsen, Martin R.; Bak, Rasmus O..
Ascorbic acid supports ex vivo generation of plasmacytoid dendritic cells from circulating hematopoietic stem cells. eLIFE 2021 ;Volum 10. s.1-21
NTNU STO

Macpherson, Alex; Laabei, Maisem; Ahdash, Zainab; Graewert, Melissa Ann; Birtley, James R.; Schulze, Monika-Sarah E.D.; Crennell, Susan; Robinson, Sarah A.; Holmes, Ben; Oleinikovas, Vladas; Nilsson, Per H.; Snowden, James; Ellis, Victoria; Mollnes, Tom Eirik; Deane, Charlotte M.; Svergun, Dmitri I.; Lawson, Alastair D.G.; van den Elsen, Jean.
The allosteric modulation of complement c5 by knob domain peptides. eLIFE 2021 ;Volum 10:e63586. s.1-27
NLSH UiO OUS UiT NTNU

Moen, Ingrid Nyhus; Westhrin, Marita; Håland, Erling; Haug, Markus; Nonstad, Unni; Klaharn, Merisa; Standal, Therese; Starheim, Kristian K..
Smac-mimetics reduce numbers and viability of human osteoclasts. Cell death discovery 2021 ;Volum 7:36. s.1-11
NTNU STO

Mohanty, Varshasnata; Subbannayya, Yashwanth; Patil, Shankargouda; Abdulla, Riaz; Mandakulutur S., Ganesh; Pal, Arnab; Ray, Jay Gopal; Sidransky, David; Gowda, Harsha; Prasad, T.S. Keshava; Chatterjee, Aditi.
Molecular alterations in oral cancer between tobacco chewers and smokers using serum proteomics. Cancer Biomarkers 2021
NTNU

Mohanty, Varshasnata; Subbannayya, Yashwanth; Patil, Shankargouda; Puttamallesh, Vinuth N; Najar, Mohd Altaf; Datta, Keshava K; Pinto, Sneha M.; Begum, Sameera; Mohanty, Neeta; Routray, Samapika; Abdulla, Riaz; Ray, Jay Gopal; Sidransky, David; Gowda, Harsha; Prasad, T S Keshava; Chatterjee, Aditi.
Molecular alterations in oral cancer using high-throughput proteomic analysis of formalin-fixed paraffin-embedded tissue. Journal of cell communication and signaling 2021
NTNU

Nilsson, Per; Johnson, Christina; Quach, Huy Quang; Macpherson, Alex; Durrant, Oliver; Pischke, Soeren; Fure, Hilde; Landsem, Anne; Bergseth, Grete; Schjalm, Camilla; Haugaard-Kedström, Linda M.; Huber-Lang, Markus; van den Elsen, Jean; Brekke, Ole-Lars; Mollnes, Tom Eirik.
A conformational change of complement C5 is required for thrombin-mediated cleavage, revealed by a novel ex vivo human whole blood model preserving full thrombin activity. Journal of Immunology 2021 ;Volum 207.(6) s.1641-1651
UiO OUS NLSH UiT NTNU

Nilsson, Per; Pettersen, Kristin; Oppermann, Martin; Skjeflo, Espen Waage; Fure, Hilde; Christiansen, Dorte; Mollnes, Tom Eirik.
Quantification of Porcine Complement Activation Fragment C3a by a Neoepitope-Based Enzyme-Linked Immunosorbent Assay. Methods in molecular biology 2021 ;Volum 2227. s.51-59
NLSH UiO UiT OUS NTNU

Niyonzima, Nathalie; Rahman, Jubayer; Kunz, Natalie; West, Erin; Freiwald, Tilo; Desai, Jigar V.; Merle, Nicolas; Gidon, Alexandre; Sporsheim, Bjørnar; Lionakis, Michail S.; Evensen, Kristin; Lindberg, Beate; Skagen, Karolina Ryeng; Skjelland, Mona; Singh, Parul; Haug, Markus; Ruseva, Marieta M.; Kolev, Martin; Bibby, Jack; Marshall, Olivia; O'Brien, Brett; Deeks, Nigel; Afzali, Behdad; Clark, Richard J.; Woodruff, Trent M.; Pryor, Mylton; Yang, Zhi-Hong; Remaley, Alan T.; Mollnes, Tom Eirik; Hewitt, Stephen M.; Yan, Bingyu; Kazemian, Majid; Kiss, Mate G.; Binder, Christoph J.; Halvorsen, Bente; Espevik, Terje; Kemper, Claudia.
Mitochondrial C5aR1 activity in macrophages controls IL-1 production underlying sterile inflammation. Science immunology 2021 ;Volum 6.(66) s.eabf2489-eabf2489
NTNU STO VV UiT NLSH UiO OUS

Ostrop, Jenny; Zwiggelaar, Rosalie Theda Margien; Terndrup Pedersen, Marianne; Gerbe, François; Bösl, Korbinian; Lindholm, Håvard Takle; Díez-Sánchez, Alberto; Parmar, Naveen; Radetzki, Silke; von Kries, Jens P.; Jay, Philippe; Jensen, Kim B.; Arrowsmith, Cheryl; Oudhoff, Menno.
A semi-automated organoid screening method demonstrates epigenetic control of intestinal epithelial differentiation. Frontiers in Cell and Developmental Biology 2021 ;Volum 8:618552. s.1-20
NTNU UiB

Chetty, Alisha; Darby, Matthew; Vornewald, Pia; Alonso, Mara Martin; Filz, Anna; Ritter, Manuel; McSorley, Henry; Masson, Lindi; Smith, Katherine; Brombacher, Frank; O'Shea, Matthew; Cunningham, Adam; Ryffel, Bernhard; Oudhoff, Menno; Dewals, Benjamin; Layland, Laura; Horsnell, WG.
Il4ra-independent vaginal eosinophil accumulation following helminth infection exacerbates epithelial ulcerative pathology of HSV-2 infection. Cell Host and Microbe 2021
NTNU

Drurey, Claire; Lindholm, Håvard Takle; Oudhoff, Menno; Maizels, Rick.
Intestinal epithelial tuft cell induction is negated by a murine helminth and its secreted products. Journal of Experimental Medicine (JEM) 2021
NTNU

Parmar, Naveen; Burrows, Kyle; Vornewald, Pia; Lindholm, Håvard Takle; Zwiggelaar, Rosalie Theda Margien; Sanchez, Alberto Diez; Alonso, Mara Martin; Fosslie, Madeleine Lystad; Vallance, Bruce A.; Dahl, John Arne; Zaph, Colby; Oudhoff, Menno.
Intestinal-epithelial LSD1 controls goblet cell maturation and effector responses required for gut immunity to bacterial and helminth infection.
PLoS Pathogens 2021 ;Volum 17.(3)
NTNU OUS

Peth, Ákos; Piecha, Dorothea; Mészáros, Tamás; Urbanics, Rudolf; Moore, Christoph; Canaud, Bernard; Rosivall, László; Mollnes, Tom Eirik; Steppan, Sonja; Szénási, Gábor; Szebeni, János; Dézsi, László.
A porcine model of hemodialyzer reactions: roles of complement activation and rinsing back of extracorporeal blood. Renal failure 2021 ;Volum 43.(1) s.1609-1620
NLSH UiT NTNU OUS

Rakner, Johanne Johnsen; Silva, Gabriela; Elschot, Mattijs; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Gierman, Lobke; Iversen, Ann-Charlotte.
The link between inflammatory and vascular pathology and sFlt-1 expression at the maternal-fetal interface in preeclampsia. Placenta 2021 ;Volum 112. s.e13-e14
UiB NTNU

Rakner, Johanne Johnsen; Silva, Gabriela; Elschot, Mattijs; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Gierman, Lobke; Iversen, Ann-Charlotte.
The link between sFlt-1 expression and inflammatory and vascular pathology at the maternal-fetal interface in preeclampsia. Pregnancy Hypertension 2021 ;Volum 25. Suppl. 1. s.e20
UiB HAUKELAND NTNU

Rakner, Johanne Johnsen; Silva, Gabriela; Mundal, Siv Boon; Thaning, Astrid Josefin; Elschot, Mattijs; Ostrop, Jenny; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Gierman, Lobke; Iversen, Ann-Charlotte.
Decidual and placental NOD1 is associated with inflammation in normal and preeclamptic pregnancies. Placenta 2021 ;Volum 105. s.23-31
NTNU UiB HAUKELAND STO

Rex, D.A.B.; Dagamajalu, Shobha; Kandasamy, Richard Kumaran; Raju, Rajesh; Prasad, T. S. Keshava.
SARS-CoV-2 signaling pathway map: A functional landscape of molecular mechanisms in COVID-19. Journal of cell communication and signaling 2021 ;Volum 15.(4) s.601-608
NTNU

Rex, D.A.B.; Deepak, K.; Vaid, Neelanchal; Dagamajalu, Shobha; Kandasamy, Richard Kumaran; Flo, Trude Helen; Keshava Prasad, Prasad.
A modular map of Bradykinin-mediated inflammatory signaling network. Journal of cell communication and signaling 2021 s.1-10
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 2021 ;Volum 73.(2) s.1-7
NTNU STO

Rogne, Tormod; Liyanarachi, Kristin Vardheim; Rasheed, Humaira; Thomas, Laurent; Flatby, Helene Marie; Stenvik, Jørgen; Løset, Mari; Gill, Dipender; Burgess, Stephen; Willer, Cristen J; Hveem, Kristian; Åsvold, Bjørn Olav; Brumpton, Ben Michael; DeWan, Andrew; Solligård, Erik; Damås, Jan Kristian.
GWAS Identifies LINC01184/SLC12A2 as a Risk Locus for Skin and Soft Tissue Infections. Journal of Investigative Dermatology 2021 ;Volum 141.(8) s.2083-2086.e8
NTNU STO

Rognes, Ingrid Nygren; Pischke, Søren Erik; Ottestad, William; Røislien, Jo; Berg, Jens Petter; Johnson, Christina; Eken, Torsten; Mollnes, Tom Eirik.
Increased complement activation 3 to 6 h after trauma is a predictor of prolonged mechanical ventilation and multiple organ dysfunction syndrome: a prospective observational study. Molecular medicine (Cambridge, Mass. Print) 2021 ;Volum 27. s.1-13
NLSH UiO OUS UIS UiT NTNU

Ryssdal, Mariell; Giskeødegård, Guro F.; Stokkeland, Live Marie T; Jarmund, Anders Hagen; Steinkjer, Bjørg; Løvvik, Tone Shetelig; Madssen, Torfinn Støve; Iversen, Ann-Charlotte; Vanky, Eszter.
Metformin mobiliserer immunforsvaret og gir færre infeksjoner hos gravide kvinner med polycystisk ovariesyndrom. Gynekologen 2021 ;Volum 3. s.79
NTNU

Ryssdal, Mariell; Vanky, Eszter; Stokkeland, Live Marie T; Jarmund, Anders Hagen; Steinkjer, Bjørg; Løvvik, Tone Shetelig; Madssen, Torfinn Støve; Iversen, Ann-Charlotte; Giskeødegård, Guro F..
Metformin changes serum cytokines in pregnant women with polycystic ovary syndrome. Pregnancy Hypertension 2021 ;Volum 25. Suppl. 1. s.e21
NTNU

Sharifi, Sina; Islam, Mohammad Mirazul; Sharifi, Hannah; Islam, Rakibul; Huq, Tahmida N.; Nilsson, Per; Mollnes, Tom Eirik; Tran, Khoa D.; Patzer, Corrina; Dohlman, Claes H.; Patra, Hirak K.; Paschalis, Eleftherios I.; Gonzalez-Andrades, Miguel; Chodosh, James.
Electron Beam Sterilization of Poly(Methyl Methacrylate)—Physicochemical and Biological Aspects. Macromolecular Bioscience 2021 ;Volum 21:2000379.(4) s.1-10
UiO OUS UiT NTNU NLSH

Sharifi, Sina; Islam, Mohammad Mirazul; Sharifi, Hannah; Islam, Rakibul; Koza, Darrell; Reyes-Ortega, Felisa; Alba-Molina, David; Nilsson, Per; Dohlman, Claes H.; Mollnes, Tom Eirik; Chodosh, James; Gonzalez-Andrades, Miguel.
Tuning gelatin-based hydrogel towards bioadhesive ocular tissue engineering applications. Bioactive Materials 2021 ;Volum 6.(11) s.3947-3961
UiO OUS UiT NTNU NLSH

Skovdahl, Helene Kolstad; Gopalakrishnan, Shreya; Svendsen, Tarjei Dahl; Granlund, Atle van Beelen; Bakke, Ingunn; Ginbot, Zekarias; Thorsvik, Silje; Flatberg, Arnar; Sporsheim, Bjørnar; Ostrop, Jenny; Mollnes, Tom Eirik; Sandvik, Arne Kristian; Bruland, Torunn.
Patient derived colonoids as drug testing platforms-Critical importance of oxygen concentration. Frontiers in Pharmacology 2021 ;Volum 12:679741. s.1-15
NTNU STO UiO UiT NLSH OUS

Sponaas, Anne-Marit; Waage, Anders; Vandsemb, Esten; Misund, Kristine; Børset, Magne; Sundan, Anders; Slørdahl, Tobias Schmidt; Standal, Therese.
Bystander memory T cells and IMiD/checkpoint therapy in multiple myeloma: A dangerous tango?. Frontiers in Immunology 2021 ;Volum 12:636375. s.1-7
NTNU STO

Stokkeland, Live Marie; Giskeødegård, Guro F.; Ryssdal, Mariell; Jarmund, Anders Hagen; Steinkjer, Bjørg; Madssen, Torfinn Støve; Stafne, Signe Nilssen; Stridsklev, Solhild; Løvvik, Tone Shetelig; Iversen, Ann-Charlotte; Vanky, Eszter.
Changes in serum cytokines throughout pregnancy in women with polycystic ovary syndrome. Journal of Clinical Endocrinology and Metabolism (JCEM) 2021 ;Volum 107.(1) s.39-52
STO NTNU

Stokkeland, Live Marie; Giskeødegård, Guro F.; Ryssdal, Mariell; Jarmund, Anders Hagen; Steinkjer, Bjørg; Madssen, Torfinn Støve; Stafne, Signe Nilssen; Stridsklev, Solhild; Løvvik, Tone Shetelig; Iversen, Ann-Charlotte; Vanky, Eszter.
Immunologiske forandringer under svangerskapet hos kvinner med polycystisk ovariesyndrom. Gynekologen 2021 ;Volum 3. s.47 NTNU

Storm, Benjamin; Christiansen, Dorte; Fure, Hilde; Ludviksen, Judith K; Lau, Corinna; Lambris, John D.; Woodruff, Trent M.; Brekke, Ole-Lars; Braaten, Tonje Bjørndal; Nielsen, Erik Waage; Mollnes, Tom Eirik.
Air Bubbles Activate Complement and Trigger Hemostasis and C3-Dependent Cytokine Release Ex Vivo in Human Whole Blood. Journal of Immunology 2021 ;Volum 207.(11) s.2828-2840
UiO NLSH NORD OUS NTNU UiT

Storm, Benjamin; Halvorsen, Per Steinar; Skulstad, Helge; Dybwik, Knut Gustav; Schjalm, Camilla; Christiansen, Dorte; Wisløff-Aase, Kristin; Fosse, Erik; Braaten, Tonje Bjørndal; Nielsen, Erik Waage; Mollnes, Tom Eirik.
Open chest and pericardium facilitate transpulmonary passage of venous air emboli. Acta Anaesthesiologica Scandinavica 2021 ;Volum 65.(5) s.648-655
UiT NLSH NORD UiO OUS NTNU

Strømme, Olaf; Heck, Kathleen; Brede, Gaute; Lindholm, Håvard Takle; Otterlei, Marit; Arum, Carl-Jørgen.
Differentially expressed extracellular vesicle-contained micrornas before and after transurethral resection of bladder tumors. Current Issues in Molecular Biology 2021 ;Volum 43.(1) s.286-300
NTNU STO

Subbannayya, Yashwanth; Di Fiore, Riccardo; Urru, Silvana Anna Maria; Calleja-Agius, Jean.
The Role of Omics Approaches to Characterize Molecular Mechanisms of Rare Ovarian Cancers: Recent Advances and Future Perspectives.
Biomedicines 2021 ;Volum 9.(10) s.1481
NTNU

Sundnes, Olav; Ottestad, William Arne; Schjalm, Camilla; Lundbäck, Peter; La Cour Poulsen, Lars; Mollnes, Tom Eirik; Haraldsen, Guttorm; Eken, Torsten.
Rapid systemic surge of IL-33 after severe human trauma: a prospective observational study. Molecular medicine (Cambridge, Mass. Print) 2021 ;Volum 27:29. s.1-10
UiO OUS UiT NTNU NLSH

Thomas, Anub Mathew; Chaban, Viktoriia; Pischke, Soeren; Orrem, Hilde Lang; Bosnes, Vidar; Sunde, Kjetil; Seljeflot, Ingebjørg; Lundqvist, Christofer; Nakstad, Espen Rostrup; Andersen, Geir Øystein; Schjalm, Camilla; Mollnes, Tom Eirik; Barratt-Due, Andreas.
Complement ratios C3bc/C3 and sC5b-9/C5 do not increase the sensitivity of detecting acute complement activation systemically. Molecular Immunology 2021 ;Volum 141. s.273-279
VV NTNU NLSH AHUS OUS UiO UiT

Thorgersen, Ebbe Billmann; Asvall, Jørund; Frøysnes, Ida Storhaug; Schjalm, Camilla; Larsen, Stein Gunnar; Dueland, Svein; Andersson, Yvonne; Fodstad, Øystein; Mollnes, Tom Eirik; Flatmark, Kjersti.
Increased Local Inflammatory Response to MOC31PE Immunotoxin After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy.
Annals of Surgical Oncology 2021
OUS UiO UiT NTNU NLSH

Thorkildsen, Marianne Thorkildsen; Mohus, Randi Marie; Åsvold, Bjørn Olav; Skei, Nina Vibeche; Nilsen, Tom Ivar Lund; Solligård, Erik; Damås, Jan Kristian; Gustad, Lise Tuset.
Thyroid Function and Risk of Bloodstream Infections: Results from the Norwegian Prospective Population-based HUNT Study. Clinical Endocrinology 2021
NTNU HNT STO

Tollefsen, Sofie Eline; Jarmund, Anders Hagen; Ytterhus, Borgny; Salvesen, Øyvind; Mjønes, Patricia; Torp, Sverre Helge.
Somatostatin receptors in human meningiomas—clinicopathological aspects. Cancers 2021 ;Volum 13.(22) s.1-13 NTNU STO

Tøndell, Anders; Subbannayya, Yashwanth; Wahl, Sissel Gyrid Freim; Flatberg, Arnar; Sørhaug, Sveinung; Børset, Magne; Haug, Markus.
Analysis of Intra-Tumoral Macrophages and T Cells in Non-Small Cell Lung Cancer (NSCLC) Indicates a Role for Immune Checkpoint and CD200-CD200R Interactions. Cancers 2021 ;Volum 13.(8)
NTNU STO

Witczak, Bartlomiej J; Pischke, Søren E.; Reisæter, Anna V.; Midtvedt, Karsten; Ludviksen, Judith K; Heldal, Kristian; Jenssen, Trond; Hartmann, Anders; Åsberg, Anders; Mollnes, Tom E..
Elevated Terminal C5b-9 Complement Complex 10 Weeks Post Kidney Transplantation Was Associated With Reduced Long-Term Patient and Kidney Graft Survival. Frontiers in Immunology 2021 ;Volum 12.
AHUS OUS NLSH UiO UiT NTNU

Yan, Bingyu; Freiwald, Tilo; Chauss, Daniel; Wang, Luopin; West, Erin; Mirabelli, Carmen; Zhang, Charles J.; Nichols, Eva-Maria; Malik, Nazish; Gregory, Richard; Bantscheff, Marcus; Ghidelli-Disse, Sonja; Kolev, Martin; Frum, Tristan; Spence, Jason R.; Sexton, Jonathan Z.; Alysandratos, Konstantinos D.; Kotton, Darrell N.; Pittaluga, Stefania; Bibby, Jack; Niyonzima, Nathalie; Olson, Matthew R.; Kordasti, Shahram; Portilla, Didier; Wobus, Christiane E.; Laurence, Arian; Lionakis, Michail; Kemper, Claudia; Afzali, Behdad; Kazemian, Majid.
SARS-CoV-2 drives JAK1/2-dependent local complement hyperactivation. Science immunology 2021 ;Volum 6.(58)
NTNU

Zelic, Matija; Pontarelli, Fabrizio; Woodworth, Lisa; Zhu, Cheng; Mahan, Amy; Ren, Yi; LaMorte, Michael; Gruber, Ross; Keane, Aislinn; Loring, Pequita; Guo, Lilu; Xia, Tai-he; Zhang, Boyao; Ørning, Mathias Pontus; Lien, Egil; Degterev, Alexei; Hammond, Timothy; Ofengeim, Dimitry.
RIPK1 activation mediates neuroinflammation and disease progression in multiple sclerosis. Cell reports 2021 ;Volum 35.(6) s.e1-e7
NTNU

Zhen, Yan; Radulovic, Maja; Vietri, Marina; Stenmark, Harald.
Sealing holes in cellular membranes. EMBO Journal 2021 ;Volum 40:e106922. s.1-13
OUS UiO NTNU

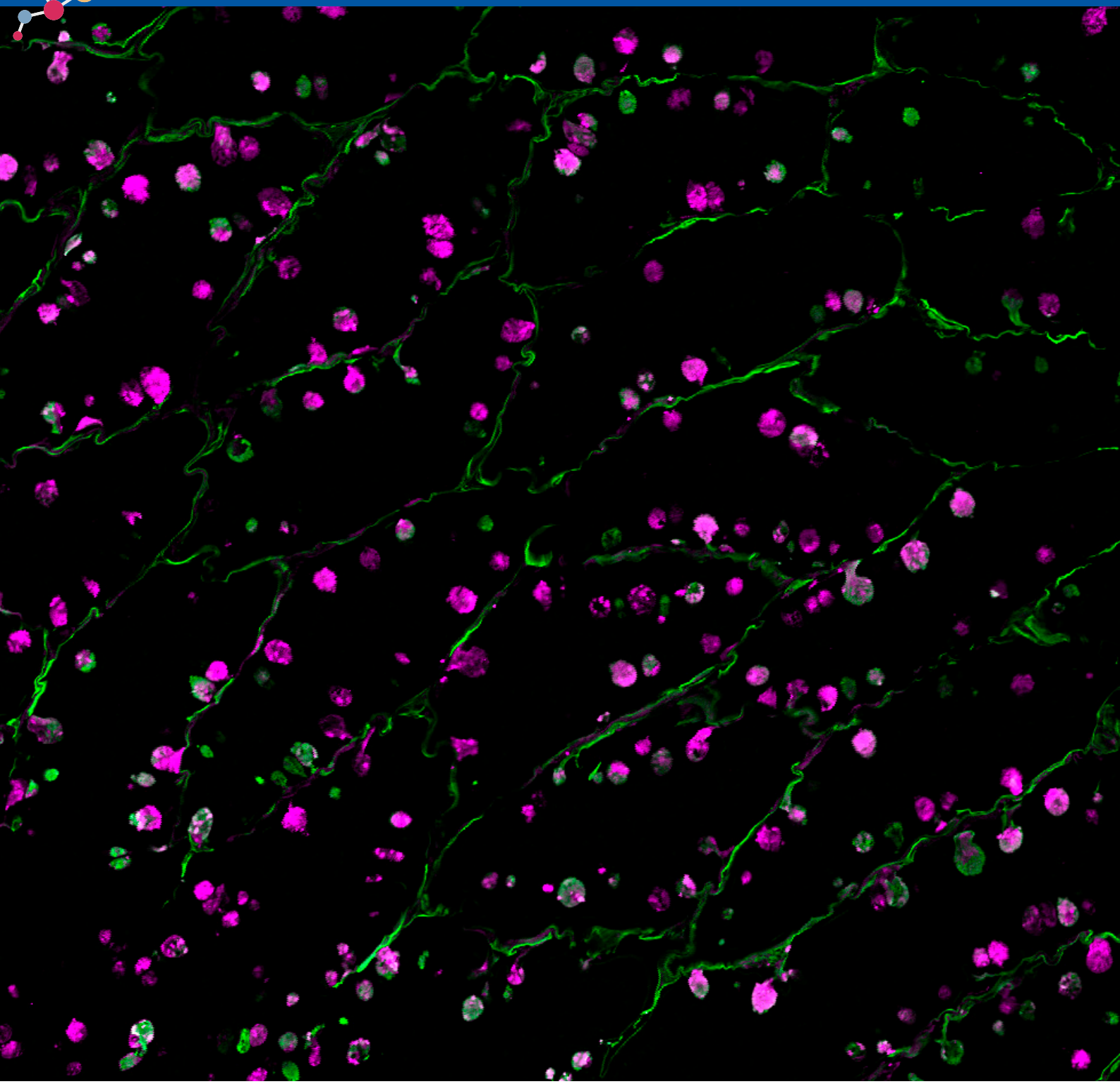
Funding and Expenditures 2021

Funding (1000 NOK)	2021
NTNU	22 929
Research Council of Norway (RCN) – Centre of Excellence grant	16 586
Other RCN funding	14 484
Other public funding	8 934
Other private funding	1 426
International funding	801
Total funding	**65 160**

Expenditures (1000 NOK)	2021
Personnel and indirect costs	48 975
Equipment	75
Other operating costs	14 245
Year result transferred to 2021	1 865
Total expenditures	**65 160**

Photo:
Page 3, 4, 6, 8, 10, 12: Geir Mogen
Page 14: Kjartan W. Egeberg, Trine A. Strand
Page 15: Nathalie Niyonzima
Page 16: Håvard T. Lindholm
Page 17, 19: Kjartan W. Egeberg
Page 18: Kristine Misund
Page 20: CEMIR
Page 21, 28: Private/CEMIR
Page 25: Kjartan W. Egeberg, Trine A. Strand, Martin Kostøl
Page 27: Helsebygg MidtNorge
Page 29, 33: Geir Otto Johansen

Page 42: 'Sugarcoating to protect against pathogens'.
'Image is a small intestinal section stained with a lectin (UEA-1, green), which binds many glycoproteins including those expressed by antimicrobial-protein expressing Paneth cells and mucus-producing goblet cells, and with an antibody against RELM-beta (magenta), a antimicrobial protein that targets Gram-negative bacteria. Induction of mucus and antimicrobials is often a key mechanism for clearing pathogens from the gut.



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