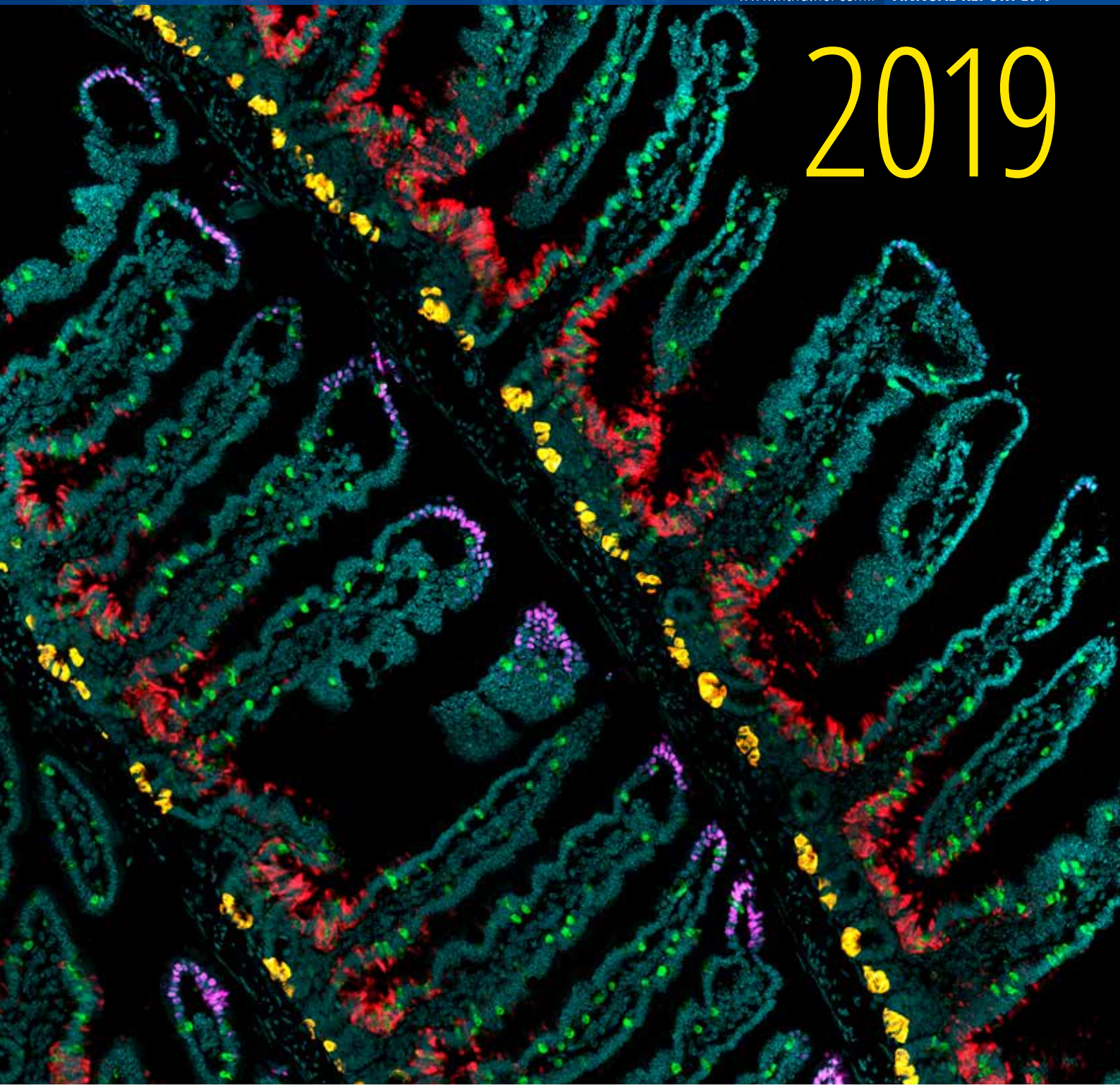
2019



Norwegian Centre of Excellence

The Research Council of Norway

CEMIR

Centre of Molecular Inflammation Research

Table of content

Cover photo:
A section of the small intestine, with the villi appearing in cyan, goblet cells in green, Paneth in orange and then some proteins related to the microbiome in Reg1 (red) and Nt5e (magenta). Alberto Diez Sanchez.

Director's comment

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

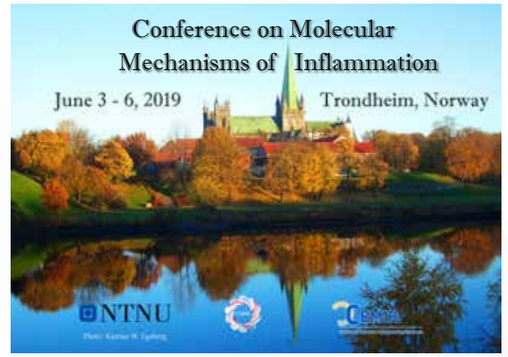
CEMIR unites scientists across disciplines to get detailed insight in basic biological- and clinical inflammation research. Looking back, there has been many productive years since the establishment of CEMIR in 2013. The first years, the main priority was to establish a unified research group in which multidisciplinary collaboration was encouraged and stimulated. To improve and strengthen the scientific quality and scope of our center two new group leaders were recruited. In 2014, all CEMIR research activities were moved to the new Knowledge Centre at Øya Campus in Trondheim, which hosts first-class laboratories with state-of-the-art cellular imaging instruments. In October 2015 we opened a new BSL3-laboratory, offering the highest level of security for research on viruses and bacteria in Norway. The new lab contains an advanced Leica SP8 confocal microscope making it possible to study infections in immune cells with viable mycobacteria and HIV virus.

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

CEMIR has grown to be a vibrant and dynamic center with 69 scientific staff members, 13 engineers, 20 students and one administrative coordinator. In 2017, CEMIR formally became a research unit in the newly established Department of Clinical and Molecular medicine. This secures the process towards a continuation of the Centre when the RCN funding ends in 2022.

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

A major highlight happened June 3rd – June 6th 2019 at the Knowledge Centre, Trondheim, when CEMIR arranged the second international *Conference on Molecular Mechanisms of Inflammation.* Twenty-four outstanding international researchers were invited to present their work,



expanding our understanding of sterile- and infectious inflammatory processes. In addition to the invited talks, 20 "short talks" were selected from abstracts and 70 posters were presented. The conference also facilitated interactions between CEMIR scientists/ students and invited speakers through "meet the speakers' lunch", poster sessions and joint meals. The conference attracted 170 participants from all over the world, and this arrangement was again a fantastic success where we were able to make CEMIR visible for the international scientific community.

The scientific activities at CEMIR have proceeded with very good progress. In 2019 68 papers have been published. CEMIR researchers have published more than 398 articles since 2013, several in high quality journals like Nature, *Nature Immunology, Autophagy, PNAS, PLOs Pathogens, Cell, Science and J Cell Biol.* Several of our papers have obtained front cover illustrations in journals. 30 CEMIR PhD students have defended their theses and successfully completed their PhDs.

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. It will be a priority for the Centre to further strengthen the collaboration with clinical departments at St. Olav's Hospital. This will help us in achieving the primary goal to identify new therapeutic targets and diagnostic tools for inflammatory diseases.

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-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.

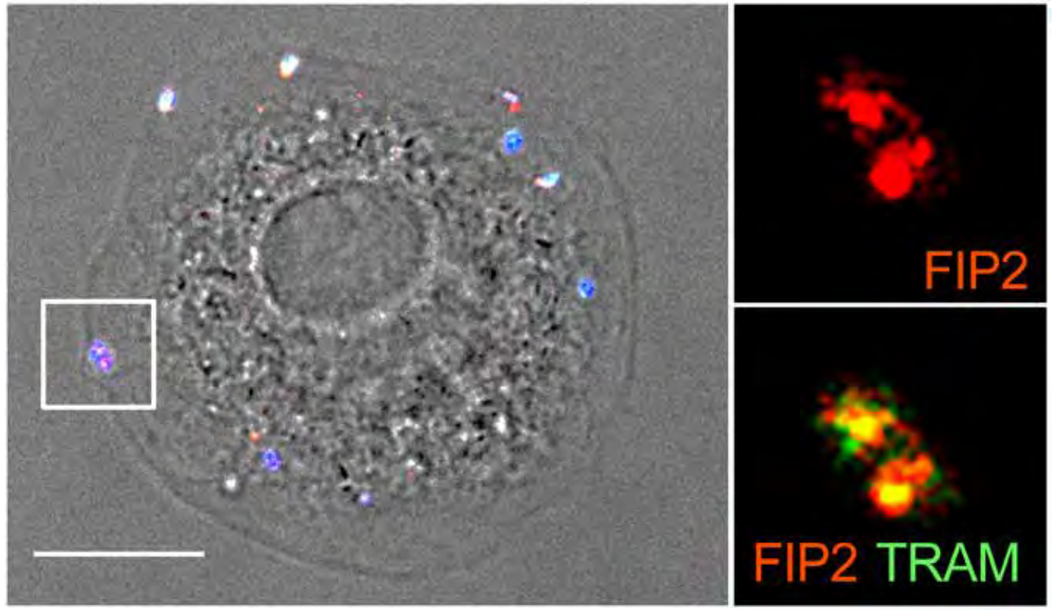
Main activities 2019

Phagocytosis is a complex process that eliminates microbes and is performed by specialised cells such as macrophages. TLR4 is expressed on the surface of macrophages and recognizes Gram-negative bacteria. Moreover, TLR4 has been suggested to play a role in the phagocytosis of Gram-negative bacteria, but the mechanisms remain unclear. In 2019 we completed and published a comprehensive study describing that the TLR4 sorting adapter, TRAM, is instrumental for phagocytosis of *E. coli* as well as for the Gram-positive *S. aureus.*

We find that TRAM forms a complex with Rab11 family interacting protein 2 (FIP2) that is recruited to the phagocytic cups of *E. coli*. This promotes activation of the actin-regulatory GTPases Rac1 and Cdc42. Our results show that FIP2 guided TRAM recruitment orchestrates actin remodeling and IRF3 activation, two events that are both required for phagocytosis of Gram-negative bacteria. A consequence of these findings is that the TRAM-FIP2 complex is instrumental in controlling both phagocytosis and TLR4-mediated TRAM-TRIF signalling from *E. coli* phagosomes. We have identified interaction domains in intracellular proteins that seem to be required to mount an inflammatory response towards Gram-negative bacteria. Based on these data we have started to construct and optimize peptides that interfere with these interactions, and subsequently inhibit inflammatory responses. These anti-inflammatory peptides may form a new treatment strategy for preventing serious host reactions towards Gram-negative bacteria.

Major achievements 2019

- Published that the TLR4 adaptor TRAM controls the phagocytosis of Gram-negative bacteria by interacting with the Rab11-family interacting protein 2 (Skjesol et al., PLOS Pathogens, 2019)
- Finalized manuscript on how plasma membrane damage caused by *M. tuberculosis* induces inflammasome activation and pyroptosis in macrophages
- Finalized manuscript on how antibiotic treatment routes *M. avium* to phagolysosomes without eliciting an immune response
- Published that TLR8 is an important sensor of pyogenic bacteria (Moen et al., Frontiers in Immunology, 2019)
- Published that phagocytosis of live and dead *E. coli* and *S. aureus* is markedly reduced by combined inhibition of CD14 and complement receptor C5aR1 (Skjeflo et al., Mol Immunol., 2019)
- Completed 1 PhD



The image shows TRAM and Rab11-FIP2 co-localization on a *E. coli* phagosome in a macrophage. Scale bar = 5µm (Skjesol et al., PLOS Pathogen, 2019).

Ambitions for 2020

- Define mechanisms how the unconventional regulators SLAMF1 and Rab11-FIP2 control TLR signaling and inflammasome activation
- Functional testing of synthetic peptides inhibiting TLR signalling in human monocytes and in whole blood
- Elucidate mechanisms and dynamics of sensing and repair of membrane damage caused by *M. tuberculosis*
- Explore the protective role of autophagy in *M. tuberculosis* infection
- Complete a study on how TLR8 and complement together regulate antibacterial responses in blood
- Delineate the mechanisms behind TLR8- and NLRP3-dependent monocyte cell death

Theme 2:

Molecular mechanisms of infection and inflammation

Theme Manager: Professor Trude Helen Flo

Despite extensive global efforts, infectious diseases still cause significant morbidity and mortality. Further, the rise in antimicrobial resistance demands the development of novel antibiotics, for which new discoveries in 'modes of infection' and 'immune evasion' are a prerequisite. In Theme 2 we aim to decipher molecular mechanisms of infection and immune 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 2019

In theme 2 we seek to understand infection mechanisms by studying both the pathogens and the host. In 2019 we finalized the work on the use of *Mycobacterium smegmatis* as a vector for efficient vaccines against mycobacterial infections. We also identified mycobacterial genetic factors required for growth under iron limiting conditions and virulence factors in the opportunistic pathogen *Mycobacterium avium*. On the host side we found that human macrophages quietly dispose of *M. avium* subject to antibiotic treatments and we are currently exploring possible host-directed therapeutics contributing to *M. avium* infection control.

There is a growing appreciation that metabolic processes and individual metabolites can shape the function of immune cells. We have discovered a protective role for an immunometabolic enzyme in *M. avium* infection and are currently exploring the underlying mechanisms. We have also performed an unbiased metabolomics screen of TLR signalling and identified several novel metabolites including an enzyme that is a potential negative regulator of type I interferon in human macrophages. Another achievement has been the establishment of a full-fledged mass-spectrometry based proteomics platform for quantitative profiling of protein expression dynamics and post-translational modifications in innate immunity. A targeted CRISPR/Cas9 screening platform has been established and successfully applied this to understanding phagocytosis of bacteria; and to identify novel genes in cell death signaling.

We have continued to study the role of the pore-forming protein gasdermin D (GSDMD) in infectious and non-infectious pyroptotic processes, and in apoptotic-pyroptotic hybrid cell death. It is becoming apparent that GSDMD is a key player in both cell death and IL-1b release, but the impact of GSDMD and its caspase1/8/11 cleavage-dead mutant D276A in vivo during infection may vary between different models. We have also clarified inflammatory/cell death roles of several novel regulators of the RIPK1/caspase-8 pathway and we are proceeding in further characterization of specific mechanisms.

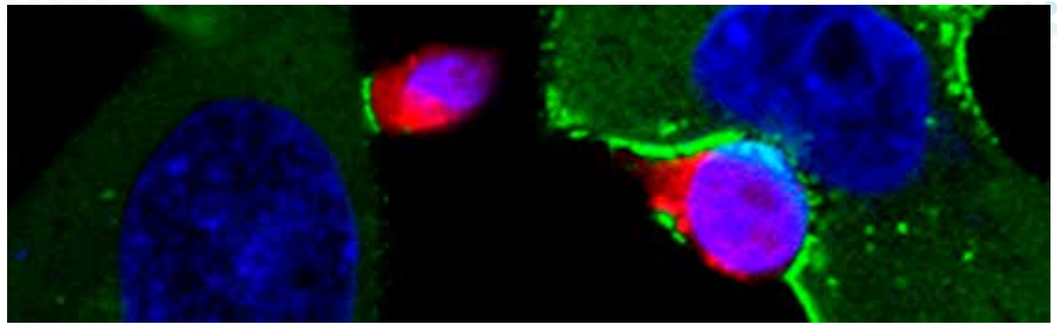
Another activity in the theme is the investigation of how reparative mechanisms are intertwined with immunity to infection. We have made effort to understand cytokine responses in intestinal epithelium using organoids, and how this relates to bacterial and helminth infection models in vivo. The helminth infection models were performed with two newly established collaborators. In addition, we have finalized a manuscript describing the detrimental role of reparative epithelium in inflammation and infection. We also have made progress in our understanding of the role Paneth cells (specialized epithelial cells that produce lots of antimicrobial products) in the maintenance of the gut microbiome.

A continued research focus this year has been on the genetic risk for invasive infections in the general population. We have now formalized collaboration with the Tromsø study and Kaiser Permanente Research Bank, USA for replicating findings from the ALL-In population in the HUNT study. We have initiated a prospective clinical study of patients with septic shock in the intensive care unit (ICU) with sampling of biological material for genetic and "omics" analyses.

PhD student Korbinian Boesl defended his thesis and graduated in 2019.

Major achievements 2019

- Identified genetic requirements for growth of mycobacteria under low iron growth conditions (Dragset et al. Scientific Reports 2019).
- Identified pathogenic genetic factors in *Mycobacterium avium* (Dragset et al. mSystems 2019).
- Published study on *M. avium* in-patient variation and virulence genes (Kannan et al., Infection and Immunity 2019).
- Determined how *Mycobacterium smegmatis* with a defective type VII secretion system ESX-3 could function as an efficient vaccine vector.
- Established tools for screening for mycobacterial proteins that influence host processes.
- Finalized the HIV-TLR8 manuscript which is accepted in Nature Communications
- Established two collaborations to perform different Helminth studies to support our organoid screening efforts.



HIV is transferred from infected cells to uninfected CD4+ T cells across virological synapses. HIV infected cells are green (the virus expresses green fluorescent protein), uninfected CD4+ T cells are red and nuclei are in blue. Photo: Marianne S Beckwith/Hany Z Meås.

- Finalized a manuscript describing the detrimental role of reparative epithelium in inflammation and infection and will submit in the first few months of 2020.
- Identified the crucial phosphatases and its interplay with kinases in immune signalling (Subbannayya et al., Int J Mol Sci. 2019).
- Identified the common cellular hijack points of viral modulation through an integrated network analysis of host-virus interactions and novel antiviral activities of broad-spectrum antiviral drugs against clinically important viruses like HCV and HMPV (Bösl, K. et al., Frontiers in Immunology 2019).
- Found important roles of GSDMD and its cleavage mutant D276A in vitro on cell death and inflammation, and in vivo on disease progression during Yersinia infection. Summary on GSDMD published (Orning et al., J Exp Med 2019).
- Identified a number of new regulators of infection-induced RIPK1/caspase-8 mediated processes in a CRISPR/Cas9 mediated screen and verified in vitro.
- Performed a mendelian randomization study of the association between Body Mass Index and risk of dying from a bloodstream infection in the HUNT population (PLoS Med, in revision).
- Identified TLR1/6/10 loci as a risk factor for sepsis through a genome-wide linkage analysis in 47 pedigrees in a population-based cohort (Crit Care Med, in revision).
- Explored the role of FER rs4957796 in risk of developing and dying from a bloodstream infection in the HUNT Study (Clin Infect Dis, submitted)
- Completed 1 PhD student

Ambitions for 2020

- Establish microscope tools for determining protein localization within mycobacteria.
- Screening 800 mycobacterial genes for potential to increase pathogenicity in the host
- Elucidate the function and potential as drug target of mycobacterial BlaR.
- Establish protocols to cultivate, differentiate and genetically manipulate induced pluripotent stem-cell (iPSC)-derived macrophages.
- Establish the impact of IRG1 and resolvins in infections with *M. avium*.
- Publish a manuscript detailing how reparative epithelium is detrimental for infectious diseases.
- Finalize a manuscript detailing a new regulator of Tuft cell differentiation in type 2 immunity against Helminths.
- Define the potential and mechanism of TLR8 ligands as HIV latency reversal agents.
- Publish the CRISPR/Cas9 screens for identification of novel host factors of HIV and Influenza A virus.
- Elucidate the molecular mechanism of novel differentially regulated metabolites identified in a metabolomics screen and publish the first manuscript on this study.
- Understanding the pro-inflammatory role of succinate by profiling the proteome succinylation landscape of innate immune signaling.
- Identify the targets of a central kinase in innate immune signalling, TBK1, through three different proteomics-centred approaches.
- Complete studies of GSDMD and its caspase-1/8/11 cleavage dead mutant D276A in bacterial type III-secretion system mediated manipulation of innate immunity.
- Complete studies of some key new regulators of the RIPK1/caspase-8 pathway, including mechanisms of action both in vitro and in vivo.
- Perform linear and non-linear mendelian randomization studies on the risk factors for invasive skin- and soft-tissue infections.
- Examine the relationship between serum lipids and lipoproteins and the risk for sepsis in HUNT and Kaiser Permanente Research Bank.
- Explore the functional role of candidate gene polymorphism from our GWAS-studies.
- Identify new sepsis trajectories and biomarkers in our ICU cohort and establish artificial intelligence (AI)-algorithms for predicting course of bacterial infections.
- Establish COVID-19 biobank and experimental models for studying SARS-CoV-2 infection.

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 have two major focuses "Inflammatory responses induced by cholesterol" and "Inflammation underlying preeclampsia and atherosclerosis". The aim is to determine pattern recognition receptor (PRR)-initiated inflammation underlying preeclampsia and cardiovascular disease. An important focus is to address the molecular mechanisms behind CC-induced inflammation in atherosclerosis. To achieve this goal, we will carry out mechanistic molecular studies, systemic analysis of inflammatory processes and patient oriented studies using clinical and biobank material.

Main activities 2019

CC are very potent activators of the extracellular complement system. In 2019 we have investigated associations between increased systemic- and local complement activation and NLRP3 inflammasome response in atherosclerosis by analyzing plasma, peripheral blood mononuclear cells and carotid plaques from patients with different degrees of atherosclerosis. We have also worked to delineate how the intracellular complement system (C5) and complement receptor C5aR1 in monocytes and macrophages participate in NLRP3 activation upon phagocytosis of CC. Moreover, studies published in 2019 demonstrate that CC possess a procoagulant feature dependent on complement and monocytic tissue factor and following plaque rupture, releasable CC may contribute to thrombosis. The use of complement inhibitors targeting either C3, C5, or C5aR1 could be an alternative clinical strategy for prophylactic treatment of atherosclerotic plaques or after thrombosis and warrants further exploration.

In 2019 we continued to dissect the contribution of the multifunctional CD5L protein to shaping the inflammatory landscape of human immune cells. Our experiments testing the nature of CD5L regulation of complement activation determined that it can inhibit the bactericidal activity of the complement. If this effect observed ex vivo is validated in vivo, it will support a new strategy to treat complement mediated autoimmune diseases that is based on control of bioavailability of endogenous proteins.

PRR activation and cholesterol accumulation is strongly associated to development of placental dysfunction at the two sites of direct maternal-fetal interaction; the uterine wall lining called the decidua and the fetal cell layer covering the placenta. Direct maternal-fetal cellular communication and atherotic lesions with foam cells are being defined in the uterine wall. Inflammasome NLRP3 and cholesterol accumulation are being identified as important players at the maternal-fetal interface. Metabolomic profiling has identified grades of placental dysfunction and is being further developed for causal classification preeclampsia and fetal growth restriction and novel biomarker selection. Novel maternal preeclampsia risk genes are being revealed in the largest meta-analysis of GWAS data in preeclampsia, performed in the EU FP7 project InterPregGen where we participate with the HUNT Study. Overall, this work has added evidence to the involvement of PRR-mediated inflammation in preeclampsia development and the mechanistic relation to cardiovascular disease, and led to discovery of underlying inflammatory mechanisms, genetic risk factors and novel predictive tools for hypertensive pregnancy disorders. Finally, we have included 200 patients in the ASSessing the effect of Anti-IL-6 treatment in MI (ASSAIL-MI) trial.

Major achievements 2019

- Published that CC induce coagulation activation through complement-dependent expression on monocytic tissue factor (Gravastrand et al., J Immunol, 2019)
- Established novel classification of placental dysfunction by metabolomics and authenticated the angiogenic factor Flt-1 as precision biomarker for pregnancies with placental dysfunction (Austdal et al., Hypertension 2019)
- Measured sensitive changes in maternal immune status during pregnancy by maternal serum cytokine profiling (Stokkeland et al., Cytokine 2019)
- Discovered that hypertensive pregnancy disorders increase the risk of maternal cardiovascular disease after adjustment for cardiovascular risk factors in a large epidemiological study combining three Norwegian health registries (Riise et al., International Journal of Cardiology 2019)
- Investigated inflammatory mechanisms and cholesterol crystal accumulation at the maternal-foetal interface

Ambitions for 2020

- Define the role for the intrinsic complement factor C5 in atherosclerosis
- Explore the interplay between serum complement and the NLRP3 inflammasome in human atherosclerosis
- Explore the systemic effects of a low-calorie restricted diet on leukocytes pattern recognition receptors, thromboinflammation and cytokines
- Determine connections between cytokines and weight-loss profiles
- Determine how CD5L controls transcriptional activity of RORα in primary human immune cells.
- Determine the mechanism by which CD5L controls bactericidal activity through the complement system
- Profile mechanisms of PRR mediated danger response at the maternal-fetal interface in preeclampsia and fetal growth restriction in relation to vascular malperfusion and other pathological processes such as oxidative stress
- Perform extensive profiling of the maternal systemic immune status during pregnancy by measuring serum cytokines in normal and complicated pregnancies
- Utilize the novel automated image-based immunohistochemistry quantification methods to identify cell specific maternal-fetal communication
- Establish causal classification of subgroups of preeclampsia and fetal growth restriction by metabolomic profiling
- Expanded collection of patient-based biobanks for translational inflammation studies
- Identify shared risk genes for preeclampsia and cardiovascular disease in HUNT and the EU FP7 project InterPregGen
- Publish the main results (6 months follow-up) from the ASSAIL-MI trial.
- Perform transcript- and lipidomic profiling during IL-6 blockade (ASSAIL-MI).
- Publish the main results (6 months follow-up) from the ASSAIL-MI trial.
- Perform transcript- and lipidomic profiling during IL-6 blockade (ASSAIL-MI).

Monocytes and cholesterol crystals (CC) are found in an intracranial thrombus retracted from a patient with advanced carotid atherosclerosis. Frozen section stained with anti-CD14/DAB and explored with polarization filter reflected light microscopy revealing birefringent CC structures using an Olympus XC30 CCD color camera, 40× objective (Gravastrand et al., J. Immunol. 203: 853–863, 2019).

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. There is a relative lack of in-depth studies of disease mechanisms in human-derived experimental models. This theme studies the IBD inflammatory process and its consequences at a mechanistic level with hypotheses generated from clinical material. In addition, there is a large focus on intestinal epithelial regenerative processes that are important in intestinal infectious and inflammatory diseases.

Main activities 2019

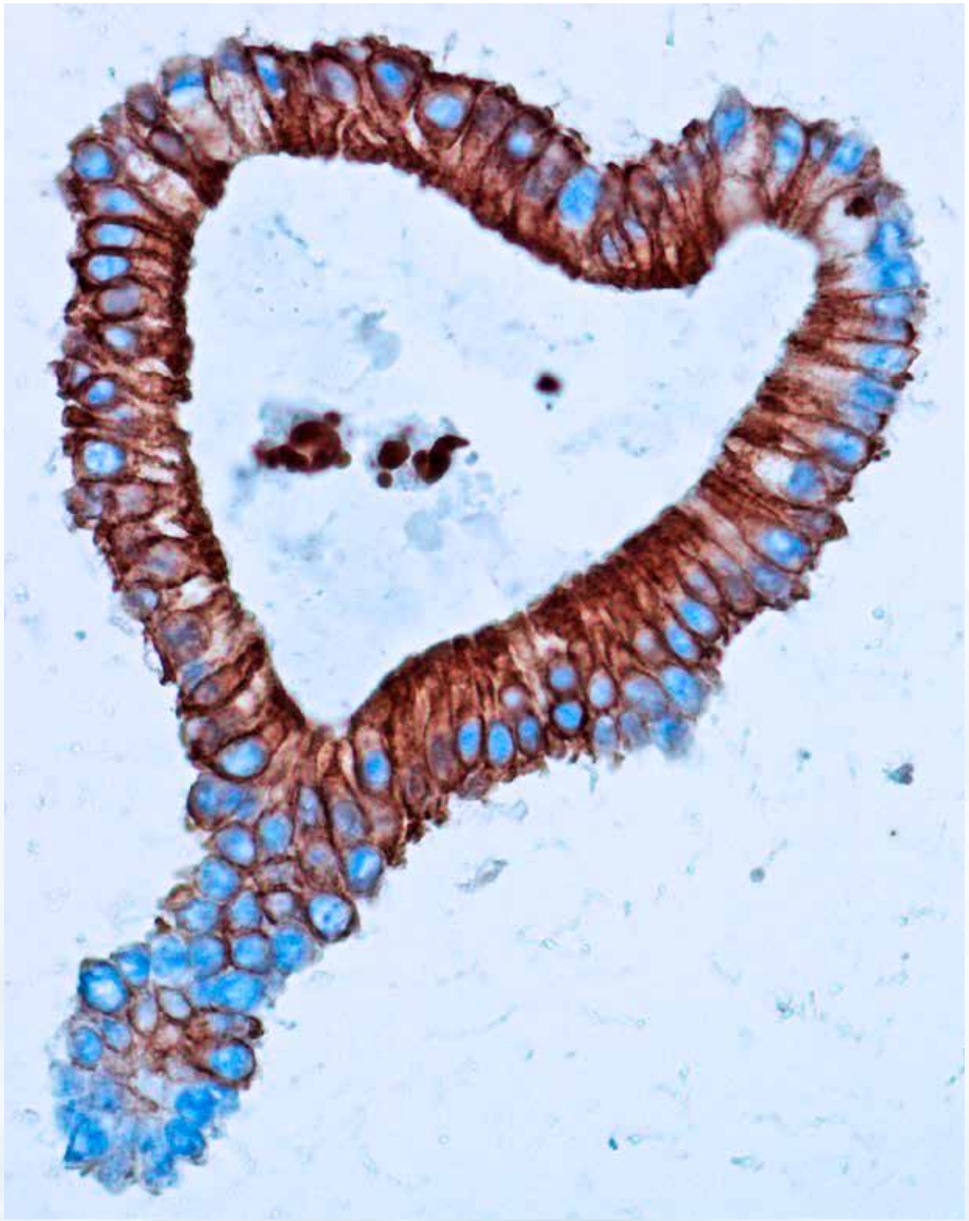
The research group has mainly examined colonic epithelial responses to immunological and physiological signals such as cytokines and chemokines. This work is being done in a collection of patient-derived colonoids and the model has been refined to work in a physiologically oxygenated environment rather than routine incubator conditions. At the same time, work in mouse organoid immune responses are being combined with relevant in vivo disease models of infection, inflammation, and repair. In addition, we are attempting to define the factors that reprogram intestinal epithelium into a reparative state and identify the cellular sources of these factors. Moreover, efforts are being made to modify colonoids by siRNA and CRISPR-Cas9 techniques, and to study the relation between gene expression and genomic variation in EQTL analyses. Of particular interest is the heterogeneous response to stimuli, which reflects the clinical problem in understanding and treating IBD. As part of this, longitudinal studies in IBD patients are ongoing to correlate clinical parameters with colonoid behavior at the level of the individual patient. These responses are e.g. studied together with collaborators to understand the role of adherent microbes (Yale collaboration) and innate $\gamma\delta$ lymphocytes (Singapore collaboration), with laboratory studies ongoing at the different sites during 2019 with two postdocs from the group visiting these.

Major achievements 2019

- Our planned activities with collaborators at Yale and in Singapore are ongoing, using IBD patient material.
- A major study on the regulation/role of ISG15 in IBD has been completed, and accepted for publication (January 2020).
- An important study on the regulation and role of LCN2/NGAL in mucosal repair, using patient material and colonoids, has been completed and published (Thorsvik et al., J Pathology 2019).
- A longitudinal treatment response study has included patients during 2019, with purpose to evaluate NGAL and innate lymphocytes as prognosis markers in addition to generating data to understand the heterogeneous response to anti TNF treatment.
- Finalized and submitted a manuscript about the epigenetic regulation of intestinal repair responses and how they relate to early life epithelial development.

Ambitions for 2020

- Finish the first project on integrating gene expression results from IBD biopsies and epithelial microdissectates with genetic variation.
- Further refine the colonoid model by establishing permanent genetically modified cultures for mechanistic studies.
- Use colonoids together with clinical material to define the role of NGAL in epithelial proliferation and mucosal repair.
- Delineate IBD-relevant immunological mechanisms originating in the epithelial cells during normoxia and hypoxia.
- Finalize a project about how intestinal smooth muscle secretes factors that can reprogram epithelium into a reparative state.
- Initiate work on how smooth muscle-derived factors define intestinal tumor progression.
- Finalize our project on how epigenetic modifiers alter epithelial cell fate decisions and/or their maturity.



A heart-shaped human colonoid immunostained with antibody against cytokeratin 20 (CK20) (brown color) marking fully differentiated surface epithelia. The nuclei are counterstained with hematoxylin (magnification 400x). Photo: Ingunn Bakke.

Theme 5:
Molecular mechanisms of inflammation in cancer progression and bone loss

Theme Manager: Professor Therese Standal

Cancer cells modulate the tumor microenvironment by secreting factors that promote chronic inflammation, inhibit immune surveillance and disrupt bone homeostasis. Pattern-recognition receptors (PRR)s are signalling immune-receptors that mediate inflammatory responses. These receptors sense pathogen or danger-associated patterns associated with stress and injury. PRRs are highly expressed on immune cells, and are promising targets in cancer immunotherapy, due to anti-tumorigenic responses they mediate in the tumor microenvironment. However, these receptors can also relay inflammatory responses in the tumor microenvironment that drive cancer progression and bone loss. Autophagy may support tumor progression by intrinsic cell mechanisms, and by cross-talks between tumor cells and stroma. **The aim of this theme is to understand interactions between tumor cells and the microenvironment at a molecular level.**

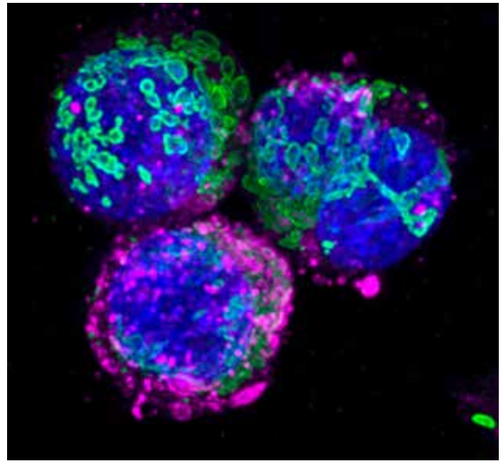
Main activities 2019

We and others have established that IL-6 secreted from cancer cells in solid tumors can induce muscle wasting and cancer cachexia in cancer patients and animal models. In 2019, we published that the secretion of IL-6 from cancer cells is controlled by an autocrine loop of the signaling compound Activin A.Targeting this loop reduced IL-6 secretion from the cancer cells and stopped weight loss in cancer bearing mice. Using another cancer model, we could publish that aggressive breast cancer development can depend on cancer cells secreting the TGFb-family antagonist GREM1. To further explore communication between cancer and stromal cells in aggressive tumours, we have established methods to isolate and characterize immune cells from aggressive and non-aggressive solid tumors.

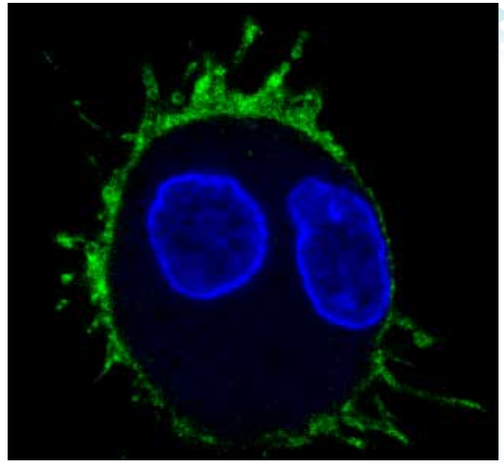
We are now in the position to combine transcriptomic, proteomics and imaging to define novel targets for reprogramming tumor immunity. In this interplay, we are particularly interested in causes and consequences of cellular starvation responses and autophagy in cancer and stroma cells.

We have observed altered PRR expression and signalling in tumor cells which may drive inflammatory responses that support metastasis. Some responses mediated by PRRs in colorectal cancer cells support the invasive ability of these cells in a PRR-dependent manner and are also upregulated in patient tumor tissue. These PRR-driven responses also support the recruitment of inflammatory immune cells to the tumor microenvironment. We have also found that some cancer cell lines secrete components that activate nucleic-sensing PRRs. We are in particular investigating components released from myeloma cells and investigating whether these components are nucleic acids, if these components are released in extracellular vesicles and what effects they can induce in cells from the tumor microenvironment.

We published that serum protein glycosylation is altered in multiple myeloma and have further studied the role of altered immunoglobulin glycosylation for bone loss in this cancer. We also studied the role of endogenously expressed, intracellular IL-32 for myeloma cell survival and proliferation. We have further elaborated the effect of IAP-inhibitors on osteoclasts, including patient material from myeloma patients, as well as extended our studies to pro- and anti-inflammatory macrophages. We have also verified the effect TAK1-inhibitors on patient myeloma cancer cells.



Myeloma cells stained for mitochondria (green), IL-32 (pink) and nucleus (blue).
Photo: Kristin Roseth Aass.



FCGROC, tekst: Pre-osteoclast stained for FCGR1 (green) and nucleus (blue).
Photo: Tonje Nedal.

Major achievements 2019

- Submitted a patent application for a 16-transcript, oxidative stress related gene expression signature in breast cancer biopsies that is a strong and independent predictor of outcome
- Published a manuscript describing a novel regulatory loop for IL-6 secretion from cancer cells in tumor with implications for how we understand, diagnose and can treat cancer cachexia (Pettersen et al., J Cachexia Sarcopenia Muscle 2020)
- Published a manuscript on the secretion of the BMP antagonist GREM1 from cancer cells in culture and in tumors that describes the control of IL-6 (Neckmann et al., Cell Commun Signal. 2019)
- Established methods for discrete genetic manipulation of cancer cells to reprogram tumor immunity
- Established experimental evidence for bioactivity of novel CSF1R inhibitors designed and synthesized at NTNU to target macrophage activation
- Submitted a collaborative manuscript describing phagocytosis of peptide decorated nanoparticles into circulating immune cells prior to their migration into solid tumour
- Discovered how apoptosis and necroptosis is differentially triggered in macrophage subtypes
- Tested that TAK1-inhibition induce cell death in myeloma patient samples
- Published a paper on altered serum protein glycosylation in multiple myeloma (Zhang et al., Biochim Biophys Acta Gen Sub 2019)
- A paper on the effect of BMP4-gene therapy in multiple myeloma was accepted for publication (Westhrin et al., JBMR Plus 2019)

Ambitions for 2020

- Publish the manuscript describing the novel oxidative stress related gene expression signature for breast cancer prognostics
- Unravel putative interactions between constitutive oxidative stress response in cancer cells and tumour immunity
- Define true NRF2 controlled genes in breast cancer cells by combining RNA sequencing of depleted cells with ChIPseq of NRF2
- Mechanistically describe how IL-6 may stimulate catabolic processes in muscle cells
- Investigate if we have alternate IL-6 protein complexes in serum with different bioactivities
- Define the interdependence of autophagy and interferon responses in cancer cells and solid tumours
- Explore if infiltrating innate immune cells may control local autophagy by inducing amino acid starvation
- Publish manuscript on IAP-inhibitors in osteoclasts
- Characterize a “gain-of-apoptosis” function in pro-inflammatory macrophages
- Test the effect of TAK1-inhibitors in a myeloma mouse model
- Publish manuscript on the role of IL-32 for myeloma cell survival
- Publish manuscript on the role of immunoglobulins for bone loss in multiple myeloma
- Publish findings on how altered PRR expression and signaling in colorectal cancer cells can promote cell migration and invasion.
- Investigate mechanisms of how PRR expression is altered in colorectal cancer and how this affects cellular responses.
- Identify the nature of the components released from myeloma cells that activate PRRs and determine how this PRR activation affects cells in the tumor microenvironment

CEMIR RESEARCH GROUPS

The Inflammation Research Group

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

The Inflammation Research group has a strong interest in applying and developing molecular and cellular imaging techniques for use in the CEMIR projects. The group leader is also scientific leader for the Imaging Core Facility at NTNU (http://www.ntnu.edu/dmf/cmic). This core facility has recently acquired the most recent state of the art confocal microscope, the LSM880 Airyscan which is very suitable for fast live cell imaging. Also, we have a 3X STED super-resolution laser confocal microscope with a PicoQuant single molecule detection upgrade, and a TIRF microscope. These three instruments are installed and well-integrated in the CEMIR laboratories.

The inflammation Research Group is collaborating with other CEMIR groups (Flo, Kandasamy and Bjørkøy) in completing the basic research oriented CEMIR themes (themes 1-4), as well as having cooperations with the more clinically orientated research themes on inflammatory bowel disease and atherosclerosis (Sandvik, Damås and Iversen).

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

The Autophagy and Oxidative Stress Defense Group

The autophagy group focuses on how this intracellular degradation route is controlled by external signaling compounds and local metabolite levels to regulate inflammation and cancer. Development and progression of solid tumors is influenced by the immune reactions in the tumors. So-called immunologically cold tumors display clear signs of local immune suppression, develop more aggressively and respond poorly to treatment. On the other side, immunologically "hot-tumors" show favorable prognosis and better responses to therapy. We, and many others, aim to find new ways to convert the local immune environment in solid tumors from "cold" to "hot". Autophagy can be highly selective degradation of intracellular proteins and organelles. Thus, autophagy has the potential to change the composition of intracellular signaling proteins in cancer and immune cells as well as other cells within and outside tumors. Activation of the Type I Interferon response is a sign of a "hot" tumor. We recently published that autophagy coincide with a dampening of the Type I interferon response in innate immune cells. We now study if immune reactions within solid tumors is controlled by autophagy. For these studies, we combine data from tumors from an immunocompetent mouse model with data mining in large databases of tumor biopsy and clinical information. The aim is to explore the idea that autophagy is a selective cellular mechanism that control tumor immunity. Innate immune cells like macrophages and neutrophils are important in solid tumors to orchestrate if the microenvironment is "hot" or "cold". Tumors dominated by anti-inflammatory macrophages indicates poor prognosis and limited effect of therapy. Formation of such macrophages depends on the macrophage specific receptor CSF1R. In a multidisciplinary collaboration, we are screening novel CSF1R inhibitors designed and synthesized by our collaborators at NTNU. The novel compounds are monitored for effects on macrophages in culture, tumors and tissues. The aim of these studies is to find different ways to target innate immune cells and reprogram the local immune microenvironment to "hot" and favorable for the patient.

Autophagy is also a way to mobilize amino acids and other nutrients during starvation. Degradation of cellular proteins is strictly controlled. Cancer cachexia is a severe complication that affect many cancer patients and is characterized by dramatic loss of muscle proteins. We have found that serum from cancer patients contain autophagy-inducing bioactivities and that this activity associates with loss in body weight. Our data demonstrate that IL-6 secreted from cancer cells induce responses in muscle cells when complexed to soluble IL-6 receptor. We have recently uncovered how TGFb-related signaling inside tumors control IL-6 secretion from the cancer cells and weight loss in tumor bearing mice. Our focus now is on how IL-6 bioactivity is regulated and how cellular responses, including stimulated autophagy, can be induced by IL-6 in cells lacking transmembrane IL-6 receptors.

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 Klebel.

The Inflammation in Pregnancy Research Group

Pregnancy is a stress test to the cardiovascular system and the hypertensive disorder preeclampsia have shared mechanisms with cardiovascular disease. The two main causative components are placental dysfunction characterized by harmful inflammation at the maternal-fetal interface and dysregulated maternal inflammatory response to the placental stress. The relation to cardiovascular disease underlies our extensive molecular studies of cholesterol driven inflammation at the maternal fetal interface, molecular characterization of atherosclerosis-like lesions in uterine wall arteries, and identification of disease specific 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 L Bjørge at Haukeland University Hospital, G Acharya at Karolinska Institute, E Vanky, K Salvesen and B Kulseng at St Olavs Hospital, T Bathen at NTNU and AK Daltveit at University of Bergen. The Research Group is partner in the 12-partner EU 7FP project InterPregGen coordinated by professor L Morgan at University of Nottingham, unravelling genetic risk factors for preeclampsia. We work closely with other researchers at CEMIR and the core facility CMIC, particularly linked to molecular studies of lipids and cholesterol crystals, danger response activation, and serum cytokine profiling.

The Research Group is led by Professor Ann-Charlotte Iversen. In 2019, the group counted 11 persons; Professor Iversen, one post doc, two PhD students, five MD PhD students, one MD student and one Staff Engineer. Two PhD and two MD PhD students completed their thesis in the group.

In 2020 our group will grow with two PhD students.

The Inflammatory Bowel Diseases (IBD) Group

The inflammatory bowel diseases (IBD) research group studies IBD pathobiology, with patient data and clinical 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. Hypotheses are generated by e.g. transcriptome analysis of biobank material from precisely characterized IBD patients; and tested in different in vitro models such as patient-derived organoids. When relevant, projects are done in close collaboration with other CEMIR groups working with e.g. innate immune mechanisms, mucosal repair and proliferation, and genome editing.

The IBD group is closely connected with clinical medicine, also through combined university/hospital positions, and collaborates with clinicians in 7 different hospitals in the Central Norway Health Region. The translational aspect was significantly strengthened in late 2019, when the group was granted CAG (Clinical Academic Group) status by the Faculty of Medicine and Health Sciences in collaboration with the Central Norway Health Authority. Work is cross-disciplinary and includes 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 animal experimental facilities, also for genetically modified mice, are available.

The group's international network includes Immunobiology at Yale University (New Haven, USA), Biomedical Sciences at Cedars-Sinai Hospital (Los Angeles, USA), Singapore Immunology Network, Biomedical Sciences Institutes (Singapore), University of Linköping (Linköping, Sweden) and Institute of Health Research (FISABIO) (Valencia, Spain).

The Bone Disease Group

Multiple myeloma is a cancer of plasma cells, located within the bone marrow. A hallmark of this cancer is the presence of a severe osteolytic bone disease, affecting nearly 80 % of the patients. The bone disease of multiple myeloma is highly aggressive, and is the cause of pain, fractures and reduced quality of life for the myeloma patients. Infections are also common, contributing to shorter life expectancy. Even though expected time of survival from diagnosis has increased significantly the last decade due to better treatment options, development of drug resistance is common, and myeloma is still considered an incurable disease. Hypoxic and ER stress and a low grade, chronic inflammation characterizes 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/or other cells in the bone marrow microenvironment. The major goals are to identify factors associated with disease progression and to understand the molecular mechanisms leading to the aggressive bone disease.

We have established a broad repertoire of protocols for differentiation of several types of bone cells from human primary cells. We have easy access to fresh, primary tumor cells from myeloma patients and our in vitro experiments are mainly performed using human primary cells. For in vivo studies we either use a traditional xenograft model allowing engraftment of myeloma cell lines, a syngeneic mouse model established in the Chesi/Bergsagel lab at the Mayo Clinic in Arizona, US, or a novel human-mouse scaffold model developed in the laboratory of Anton Martens, the Netherlands. This model allows for a reconstruction of a human hematopoietic environment in scaffolds that are subsequently implanted in immune compromised mice. The model aslo allows for engraftment of primary cells from patients. We have equipment to follow tumor growth in vivo by near near-infrared fluorescent protein-based imaging or bioluminescence. The acquirement of a mCT machine at the animal facility as well as a collaborative effort together with the osteoporosis group at NTNU (headed by professor Unni Syversen) to establish a bone histomorphometry laboratory has further strengthen our opportunities in terms of bone quality assessments.

The group is led by professor Therese Standal and currently consists of four PhD students, a post doctor, a researcher and a technician. Our group profits from a close collaboration with clinicians and researchers at the Center of myeloma research, NTNU. We collaborate closely with the Hematology Department at St. Olavs Hospital, the Regional Biobank (Biobank1) and the Nordic Myeloma Study Group.

Cellular and Molecular Mechanisms in Regeneration

Tissue repair is required to recover from insults such as caused by inflammation or infection. A lack of repair can result in the development of chronic infectious or inflammatory diseases. Furthermore, unattended inflammation or aberrant repair can also lead to neoplastic lesions. Our group studies these reparative responses using both in vivo and ex vivo (organoid) models of disease. Our primary organ of interest is the gut. We have different focus areas in our lab. For example, we capitalize on CEMIR's impressive imaging infrastructure to develop (imaging) techniques to analyze tissue and organoid microscopy. Biologically, we are interested in how intrinsic epithelial factors regulate repair responses, and how this is linked to early-life intestinal epithelial development. In addition, we study how niche factors derived from stromal or other cell types affect repair after inflammation and how this relates to tumor formation. Finally, we aim to determine how immune factors such as cytokines affect epithelial responses and how this is intertwined with abovementioned niche factors during bacterial and parasitic infections.

We currently have a range of collaborators for our different research lines. Our collaborators contribute with their own unique knowledge, reagents, models, or techniques to help us meet our research goals. Dr. Toshiro Sato (Keio University, Tokyo) is our collaborator for using human organoid disease models. Dr. Maarten Altelaar (Utrecht University, The Netherlands) provides his expertise in Mass Spectrometry to quantify non-histone methylation in cellular signalling. We have established a collaboration with the group of Dr. Kim Jensen (The BRIC, Copenhagen, Denmark) to help comparing foetal and regenerative epithelium. In addition, we are working with the groups of Drs. Rick Maizels (University of Glasgow, UK), Kathryn Else (University of Manchester, UK), and William Horsnell (University of Cape Town, South Africa) to study helminth infection models in different projects. Nationally, we work together with John Arne Dahl (Oslo) to perform ChIP-sequencing experiments in our work on the epigenetic regulation of the intestinal epithelium. Finally, within NTNU, Finn Drabløs co-supervises one of the PhD students to provide support to analyze RNA and ChIP sequencing using bioinformatics.

This group started in 2016, is led by Menno Oudhoff, and in 2019 consisted of 4 Postdocs, 3 PhD students, 3 MSc students, and 1 Research Assistant. Although we have not formally published our studies, we finalized two studies in 2019, and in 2020 we anticipate finalizing 3 more studies that we hope to all publish in 2020.

The Myco-HIV Research Group

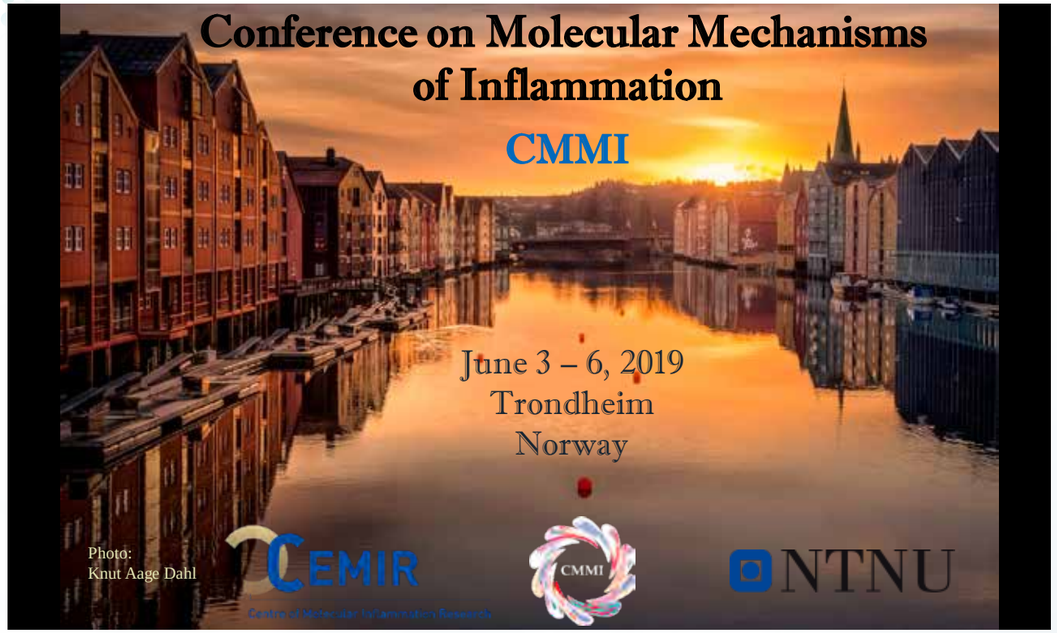
Mycobacteria and HIV can cause life-long infections and pose a global health challenge. Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), kills about 1.7 million people each year and the prevalence of non-tuberculous mycobacterial infections caused by *M. avium* is increasing in individuals who are immunocompromised due to underlying disease or use of immunosuppressant drugs. Mycobacterial infections require long treatment with antibiotics, and drug resistant strains are emerging. Our primary research focus is the molecular host defense mechanisms involved in immunity to mycobacterial pathogens and virulence strategies employed by mycobacteria to parasitize host cells. Intracellular trafficking, compartmentalized pattern recognition receptor signaling, host cell killing and nutrient metabolism are central for survival and attractive targets for drug development, and are currently investigated in our lab in the host and in the pathogen. We are studying innate properties of the T-cell responses to HIV. T-cells express PRRs and respond to microbial ligands with cytokine production. The significance of this in HIV disease is currently not understood and something we are interested in. In collaboration with the Systems Inflammation group we also do CRISPR-screens to reveal host factors central for HIV defense and virulence. We believe our basic research strategy may contribute to revealing new therapeutic targets and adjunct host-directed therapies, as well as in vaccine development.

The Research Group is led by Trude H. Flo and includes four more research scientists, two post docs, four PhD students, one medical research student and master students. We have developed expertise, methods and tools to study HIV, mycobacteria and the host innate and adaptive immune defenses both in vitro in human primary cells and cell lines, and in vivo in mice. 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 imaging of Mtb and HIV infections. Transposon mutant libraries with more than 150 000 mutants in *M. smegmatis*, *M. avium* and Mtb are available. We collaborate closely with the systems inflammation group (R Kandasamy), the inflammation group (T Espevik, JK Damås) and with CEMIR affiliated professors D Underhill (Cedars Sinai, infection biology) and H Stenmark (OUS, membrane trafficking). We also pioneer the use of Focused Ion-Beam Scanning Electron Microscopy at NTNU Nanolab to perform high resolution imaging of intracellular infections. Central external collaborators are P Sikorski (NTNU, physics/nanotech), K Tasken (OUS, T-cells), Anne Simonsen (UiO, autophagy), AM D Riise (OUS, TB & HIV), E Rubin (Harvard, mycobacteria), R Brosch (Institut Pasteur, mycobacteria), N Reiling (Research Center Borstel, mycobacteria), K Prasad (Yenepoya University, proteomics), M Lerm (Linkøping University, TB screens), M Niederweis (Univ Alabama, Mtb).

The Systems Inflammation Research Group

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

The research group led by Richard K. Kandasamy currently includes 1 Ph.D. student, 3 post-docs and 1 Masters student. We work in close collaboration with CEMIR research groups led by Terje Espevik and Trude H. Flo; as well as Per Bruheim (Department of Biotechnology, NTNU), Denis Kainov (Department of Clinical and Molecular Medicine, NTNU) and Geir Slupphaug (NTNU Proteomics Core). Our international collaborators include Kate Fitzgerald (UMASS Medical School, Worcester, USA), Egil Lien (UMASS Medical School, Worcester, USA), Giulio Superti-Furga (Center for Molecular Medicine, Vienna, Austria), Christoph Bock (Center for Molecular Medicine, Vienna, Austria), André Müller (Center for Molecular Medicine, Vienna, Austria), Rune Linding (University of Copenhagen, Copenhagen, Denmark), Keshava Prasad (Center for Systems Biology and Molecular Medicine, Yenepoya University, Mangalore, India), Min-Sik Kim (Kyung Hee University, Seoul, South Korea) and Akhilesh Pandey (Johns Hopkins University, Baltimore, USA).



Opening of the conference by Dean at the Faculty of Medicine and Health Sciences Björn Gustafsson.

Håvard Lindholm received a travel grant for "best poster".

Conference gala dinner at Restaurant Jossa.

The second international conference on molecular inflammation in Trondheim

June 3rd – June 6th CEMIR organized the second international conference on mechanisms of molecular inflammation. The conference brought together scientists from basic and clinical research who provided us with several interesting talks and posters with significant insight into common underlying processes of inflammation in sterile and infectious diseases.

The conference attracted 170 participants from all over the world, including 24 outstanding invited speakers, 20 short talk speakers selected from abstracts, and 70 poster presenters. The presentations covered cutting edge highlights within the categories innate cell biology, inflammatory signaling pathways, inflammations in cancer progression and bone loss, intracellular infections, inflammatory cell death, cell intrinsic defenses and compartmentalized signaling, complement and cardiovascular disease and gut inflammation. The high-quality presentations inspired to scientific discussions in the auditorium, during the organized "speakers' lunch", the poster session and at the various social events that took place during the conference. An external committee selected the three best posters and two best short talks which were rewarded with travel grants (sponsored by Science Immunology) or journal subscriptions (Nature Review Immunology). The CEMIR-members Håvard Lindholm, Caroline Gravastrand and Kristine Pettersen received the three poster awards.

The conference was covered by the local press NRK Trøndelag and Adresseavisa. Also, one issue of the Journal of Leukocyte Biology (JLB) will be dedicated to the conference, with contributions from the invited speakers.

This successful conference managed for the second time to draw international attention to the CEMIR community and this important field of research.

GUEST LECTURES IN 2019

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

March 5th, Associate Professor of Immunology Alexander Drakesmith, University of Oxford, UK:
Iron, infection and anemia: Evolutionary viewpoints on a huge global health problem.
(Opponent at the PhD-defense of Ulrike Neckmann.)

March 25th, Professor Andrew Macpherson, University Hospital in Bern, Switzerland:
The Microbiota, its Metabolites, and the Mammalian Host.
(This seminar was supported by IKOM, CEMIR and the Norwegian Society for Immunology.)

May 2nd, Professor Søren Riis Paludan, Aarhus University, Denmark:
Sensing of foreign DNA by the cGAS-STING pathway in innate immunity.
(Opponent at the PhD-defense of Korbinian Bösl.)

May 2nd, Researcher Tuula Anneli Nyman,
Head of Proteomics Core Facility at University of Oslo, Norway:
Extracellular vesicles in innate immune response.
(Opponent at the PhD-defense of Korbinian Bösl.)

May 8th,
Professor Katherine Fitzgerald,
UMass, USA:
Regulation of Inflammation by nucleic acid binding proteins.
(In connection with MOL8006 PhD course.)

May 13th,
Professor Harald Stenmark,
UiO/CEMIR, Norway:
ESCRT proteins in membrane dynamics.
(In connection with MOL8006 PhD course.)

June 19th, Dr. Elizabeth Mann, University of Manchester, UK: *Regulation of Mucosal Macrophage Function by the Microbiota.*
(Examiner, MSc Molecular Medicine.)

June 25th, Dr. Pekka Katajisto, University of Helsinki, Finland, and Karolinska Institute, Sweden: *Stem Cells and Aging.*
(Examiner, MSc Molecular Medicine.)

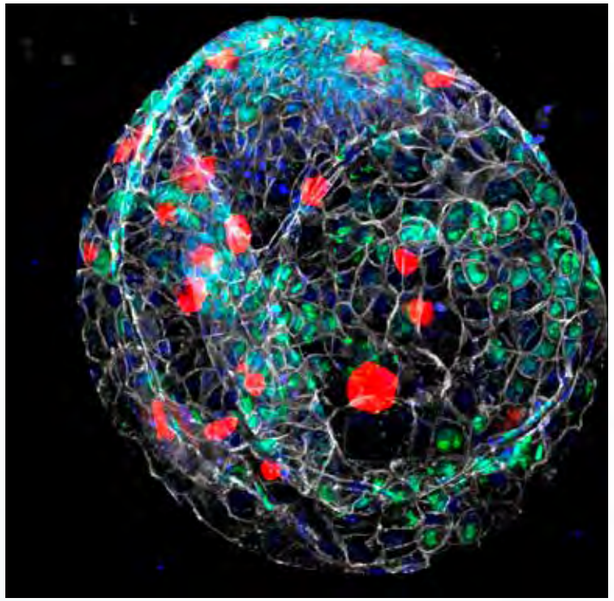
Aug 20th, Even Holth Rustad, Memorial Sloan Kettering Cancer Center, New York, USA: *Timing the initiation of multiple myeloma.*
(In connection with Even Holth Rustad's defence.)

October 9th, Professor Judith Allen, Lydia Becker Institute of Immunology and Inflammation University of Manchester, UK

October 29th,
Professor David Underhill,
Cedars-Sinai, Los Angeles, USA:
Harnessing anti-fungal immunity for a better Staphylococcus aureus vaccine.
(In connection with MOL8010 PhD course.)

November 1st, Gabor Horvath, the Microscope Core Facility, Bonn University, Germany: *Harnessing anti-fungal immunity for better Staphylococcus aureus vaccine.*
(At the annual CEMIR seminar, and in connection with PhD course MOL8010.)

CEMIR USE OF THE IMAGING CORE FACILITY



Mouse small intestinal organoids stained for Ki67 as a proliferation marker (green), UEA1 to see goblet cells (red), β- catenin (grey) and counterstained with DAPI (blue). Objective: 20 X Contribution.
Photo: Naveen Parmar and Håvard Takle Lindholm.

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.

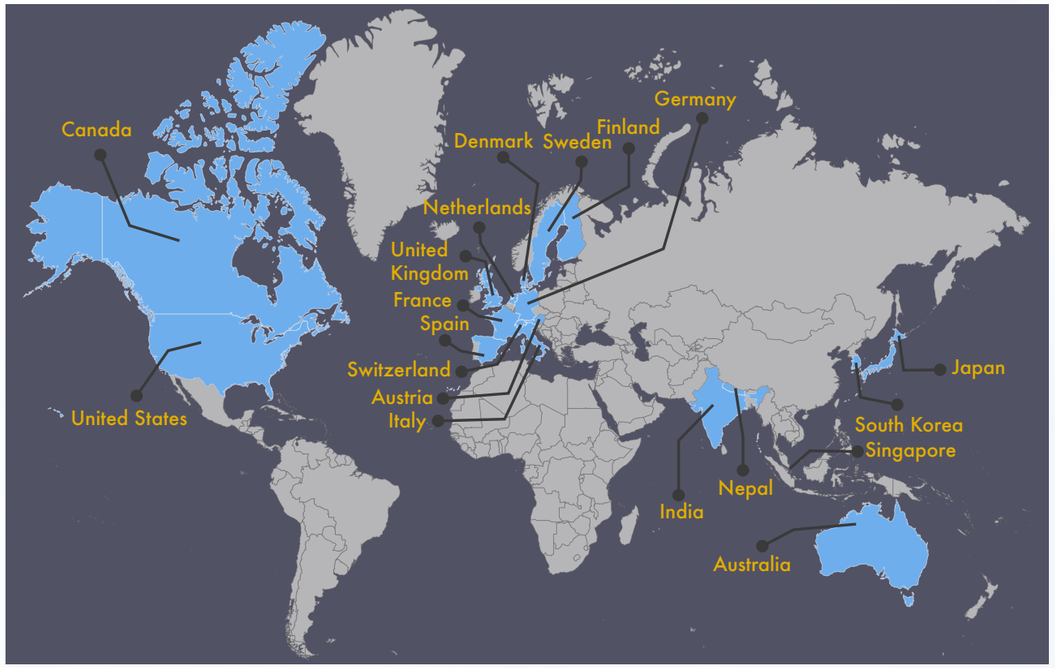
Researchers and students at CEMIR have access to a multitude of different imaging techniques, for live cell studies as well as imaging of fixed cells and tissue preparations. These instruments are all part of the Cellular and Molecular Imaging Core Facility, CMIC, at Faculty of Medicine, NTNU, www.ntnu.edu/mh/cmic. 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.

January 2019 a Zeiss LSM 880 Airyscan super resolution confocal microscope was installed at CMIC. This microscope uses a special 32 array GaAsP PMT detector to collect more light from the sample for each pixel, resulting in an image with better resolution and greater signal efficiency. In combination with state-of-the-art deconvolution we can achieve resolution down to about 80 nm, which is over two times better than conventional confocal microscopes. The array detector can also be used in "fast" mode for high speed, high resolution live cell imaging. The instrument is otherwise well equipped with an incubator system for controlled temperature and CO2 environment. The Zeiss Zen Connect software can be used to combine and correlate data from other microscopes and modalities, such as electron microscopy for a better understanding of your samples. This instrument has been highly utilized by CEMIR students and researchers during 2019.

Furthermore, CMIC has a high-end Leica SP8 STED 3X super-resolution microscope with the possibility to perform single molecule detection and analysis that is particularly useful for studying molecular interactions in cells. This confocal microscope also has a Hamamatsu Orca-Flash 4.0, and in combination with new Leica Navigator software, this enables high speed fluorescence images for screening and overview. High content imaging is also possible on a Zeiss TIRF III fluorescence microscope equipped with a new Hamamatsu Orca-Fusion camera. Rapid and initial fluorescence screening is now available on rebuilt Zeiss Axiovert 200M with a new PCO camera plus a CoolLED light source.

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

INTERNATIONAL COLLABORATION



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

Six outstanding professors from other institutions are affiliated with CEMIR: Kate Fitzgerald and Egil Lien from UMass Boston, David Underhill from Cedars-Sinai LA, Eicke Latz from Univ. Bonn, and Harald Stenmark and Tom Eirik Mollnes from Oslo University Hospital. They work in the fields of cell biology and innate immunity and contribute extensively to the research programme 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, England, Spain, Germany and Scotland.

English is our daily working and teaching language
33% of the CEMIR staff is international (53% of PhD candidates and post docs), representing more than 15 different countries.

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

COOPERATION WITH CLINICAL DEPARTMENTS

Arne Sandvik and Ann Elisabeth Østvik were awarded the "CAG IBD" at Kunnskapssenteret December 2nd. From left: Rector Anne Borg, Arne Sandvik, Ann Elisabeth Østvik and Director of the Central Norway Regional Health Authoritiy, Stig Slørdahl.

The vision of CEMIR is to lay the foundation for novel therapies and diagnostic tools for inflammatory diseases through research in molecular innate immune responses. We seek to identify and explore inflammatory pathways in various infections, atherosclerosis/preeclampsia, multiple myeloma and inflammatory bowel disease (IBD), that later may be exploited in development of novel therapeutic approaches as well as can serve as both diagnostic and predictive markers for these diseases. We believe that these "inflammatory signatures" will be essential in establishing individualized medicine algorithms in these disorders. To achieve this, we have established a close collaboration between CEMIR and St. Olav's Hospital, both institutions located at Øya Campus. Several of our staff members are employed at both the hospital and NTNU.

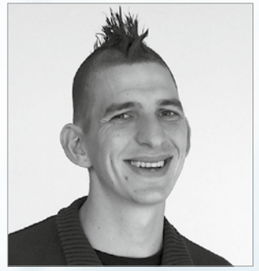
Several papers from 2019 include analyses of clinical materials, further establishing the clinical relevance of basic inflammatory processes. We have published several studies using clinical samples from both biobanks and interventional studies. We have access to the clinical and genetic data from the large genotyped population-based HUNT2 study linked with our Mid-Norway Sepsis Register. The IBD-group at CEMIR was announced a clinical academic group (CAG) in 2019. A CAG is an academic clinical research group, which consist of researchers and clinicians from the NTNU and St Olav's hospital. A CAG contributes to the health sector with new research and increased quality within the field of clinical practice. This will be achieved through a strong professional network with a joint strategic aim across healthcare settings from CEMIR and the health region.

COMPLETED PHDs in 2019

for the degree of Philosophiae Doctor

Ulrike Neckmann
defended her thesis *The Identification of Features of Aggressive Breast Cancer* Development March 5, 2019. Her supervisors have been Professors Geir Bjørkøy and Trude Helen Flo, and researcher Tonje Strømmen Steigedal.

Silje Thorsvik
defended her thesis *Neutrophil gelatinase-associated lipocalin in inflammatory bowel disease* April 5, 2019. Her supervisors have been Professors Arne Kristian Sandvik and Jan Kristian Damås, and Associate Professor/MD Ann Elisabeth Østvik.



Korbinian Bösl
defended his thesis *Novel insights on human-virus interactions through genome-wide approaches* May 3, 2019. His supervisors have been Associate Professor Richard Kandasamy and Professor Terje Espevik.

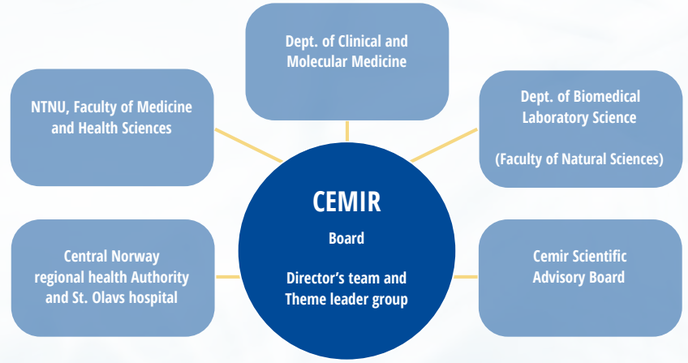
Birgitta Ehrnstrøm
defended her thesis *Exploring the role of TLR8 as a sensor in bacterial infections* December 13, 2019. Her supervisors have been researcher Jørgen Stenvik and Professor Jan Kristian Damås.

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 providing 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 2019.

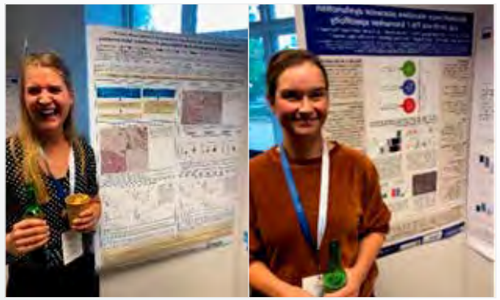
From 2018 the board members are:
Torstein Baade Rø – *(Board chairman) Head of Dep. of Clinical and Molecular Medicine, NTNU*
Pål Romundstad – *Vice Dean, Faculty of Medicine and Health Sciences, NTNU*
Lars Gunnar Landrø – *Head of Dep. of Biomedical Laboratory Science, NTNU*
Gilda Susan Opland – *Head of clinic, Clinic of Laboratory Medicine, St.Olavs Hospital*

CEMIR Scientific Advisory Board (SAB)
One SAB meeting was held in 2019.

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



From the ISSHP conference at Lund where the pregnancy group presented their research.

Trude gave a very nice presentation about antibiotic resistance as part of *The Art and Knowledge: Aksnes & Moen and Trude Helen Flo* during The Big Challenge festival. This was done in connection to the artist duo's exhibition The Micro Challenge.

Forsker Grand Prix: Håvard Lindholm, a PhD student in the Oudhoff group, participated in the regional final of the Forsker Grand Prix at Byscenen September 26.
Photo: Thor Nielsen, CC BY-SA 2.0.

CEMIR members contributed with more than 60 posters and oral presentations at conferences in 2019, such as

- Conference on Molecular Mechanisms of Inflammation
- Keystone - Helminths: New Insights from Immunity to Global Health
- European ISSHP Conference
- Seeing is Believing - Imaging the Molecular Processes of Life
- The 4th Turning the Tide of Antimicrobial resistance meeting
- Norwegian Biochemical Society 55th Contact Meeting
- Gordon Research Conference on Tuberculosis Drug Discovery and Development
- 12th International Conference on Complement Therapeutics
- Copenhagen Bioscience Conference – Intestinal organoids
- FIRM – reisemedisinkonferanse
- International Symposium on Discovery of Actionable Targets in Infectious Diseases
- IUIS2019 17th International Congress of Immunology
- 45th Annual Meeting of the Scandinavian Society for Immunology (SSI)
- Studentkonferansen Frampeik
- American association for bone and mineral research annual meeting
- Herbert Fleisch workshop

VG had a large article about the research of Kristine Pettersen, Sonja Andersen and Geir Bjørkøy September 7th, including main notice on the front page. Gemini, Teknisk Ukeblad and ABC Nyheter also covered the publication of this research:

Radio, blog and podcast:

Astrid Skjesol wrote about the PLOS Pathogens article in the blog #NTNUmedicine (June 21.).

Trude Helen Flo talked about Inflammation at NRK Trøndelag Radio June 5th.

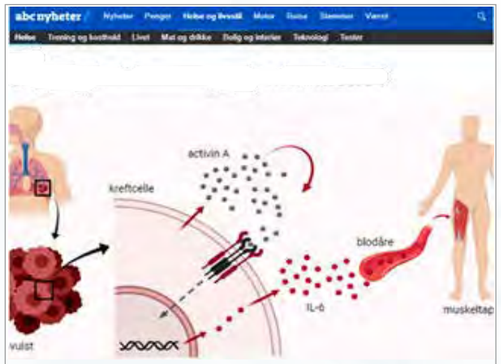
She also made the podcast "Diagnose» about antibiotic resistance which was published October 24th.

From the newspaper:


SLIK SPISER KREFT MUSKLENE

Ny forskning avslører: Én av tre dør ikke av sykdommen i seg selv

VG had a large article about the research of Kristine Pettersen, Sonja Andersen and Geir Bjørkøy September 7th, including main notice on the front page.



En kreftsvulst kan få muskelceller i kroppen til å bryte ned seg selv. Mange kreftpasienter dør av følgene. Nå vet vi mer om hvordan kreftceller i en svulst kan forsake en slik tilstand.

Gemini, Teknisk Ukeblad and ABC Nyheter also covered the publication of this research.

A publication of the research by Anne Mari Rokstad, Caroline Gravastrand and coworkers received publicity in Gemini and Norwegian SciTech News. (September 22nd.)

Betennelse – et tveegget sverd for helse og sykdom

Hva har betennelse med overvekt, kreft og Alzheimers sykdom å gjøre? Jo, ganske mye skal det vise seg.

June 5th – during the CEMIR conference – Trude and Terje had a nice chronicle in Adresseavisa about inflammation.

Awards/Prizes:

- Håvard Lindholm, Caroline Gravastrand and Kristine Pettersen received poster prizes at the Conference on Molecular Mechanisms of Inflammation in June.
- Marita Westhrin received the prestigious "young investigator award" for her immunoglobulin project at the big ASBMR (American association for bone and mineral research) conference in September.
- Sindre Ullmann won the poster prize at the conference Turning the tide against antimicrobial resistance in November.

INNOVATIONS AND PATENTS

Innovation strategies for controlling inflammatory diseases

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. Harmful inflammatory responses may also occur during cancers and this response may increase the tumor cell growth. Thus, there is a need for identifying new targets and new strategies for controlling inflammatory responses.

At CEMIR we currently have two innovation strategies for controlling inflammation. The first one is to control inflammation by interfering with the Toll-like receptor 4 signaling pathway. The Inflammation group headed by CEMIR director Terje Espevik has identified interaction domains in two intracellular proteins that are required to mount an inflammatory response towards Gram-negative bacteria. Based on these data we have constructed peptides that interfere with the interaction of the two proteins. The peptides have strong inhibitory effects on cytokine production induced by Gram-negative bacteria and may form a new treatment strategy for preventing serious host reactions to bacteria leading to sepsis. The Norwegian Research Council supports the project through an "optimization" grant, and a patent application is being filed.

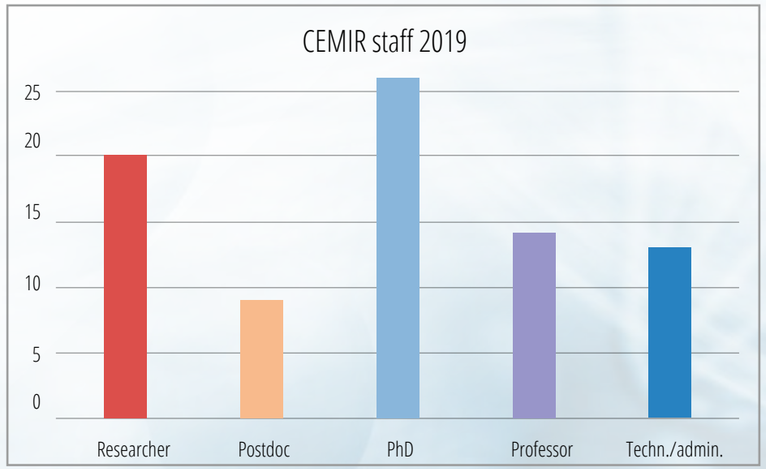
The other innovation strategy is to control inflammation by interfering with the colony stimulating factor 1 receptor (CSF1R). The tyrosine kinase receptor CSF1R, specifically expressed on monocyte-derived cells, is crucial for differentiation and survival of macrophages including bone-degrading osteoclasts.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

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

CEMIR STAFF 2019

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 2019 69 scientific staff members, 13 engineers, 20 students and one administrative coordinator were associated with the Centre.



Name		Position	Nationality	Research group
Aas	Kristin Roseth	PhD candidate	Norway	Bone disease
Alonso	Mara	Postdoctor	Spain	Regeneration
Andersen	Sonja	Staff engineer	Norway	Support group
Bakke	Siril Skaret	Postdoctor	Norway	Inflammation
Bjørkøy	Geir	Professor	Norway	Autophagy
Boyartchuk	Victor	Researcher	Ukraine	Inflammation
Buene	Glenn	Staff engineer	Norway	Bone disease
Bugge	Marit	Postdoctor	Norway	Bone disease
Cemalovic	Ena	PhD candidate	Bosnia-Hercegovina	Inflammation
Damaas	Jan K	Professor	Norway	Inflammation
Diez	Alberto	Postdoctor	Spain	Regeneration
Dragset	Marte Singsås	Researcher	Norway	Mycobacteria and HIV
Egeberg	Kjartan	Staff engineer	Norway	Inflammation
Ehrnstrøm	Birgitta	PhD candidate	Sweden	Inflammation
Espevik	Terje	Professor	Norway	Inflammation
Fitzgerald	Kate	Professor II	UK	Inflammation
Flo	Trude Helen	Professor	Norway	Mycobacteria and HIV
Giambelluca	Miriam	Postdoctor	Spain	Systems inflammation
Gidon	Alexandre	Researcher	France	Mycobacteria and HIV
Gierman	Lobke	Postdoctor	Netherlands	Pregnancy
Granlund	Atle Van Beelen	Researcher	Norway	IBD
Gravastrand	Caroline	PhD candidate	Norway	Inflammation
Haug	Markus	Researcher	Germany	Mycobacteria and HIV
Husebye	Harald	Researcher	Norway	Inflammation
Håland	Kari	Head of administration/ Staff engineer	Norway	[From Jan-Aug 2019]
Iversen	Ann-Charlotte	Professor	Norway	Pregnancy
Johansson	Ida	Postdoctor	Norway	Autophagy
Johnsen	Ingvild Bjellmo	Researcher	Norway	Mycobacteria and HIV
Kandasamy	Richard Kumaran	Associate professor	India	Systems inflammation
Kastnes	Martin	PhD candidate	Norway	Bone disease
Kim	Hera	PhD candidate	South-Korea	Systems inflammation
Kojen	June Frengen	Staff engineer	Norway	Support group
Kovcic	Vlado	PhD candidate	Croatia	Bone disease
Lamsal	Apsane	PhD candidate	Norway	Autophagy
Latz	Eicke	Professor II	Germany	
Lian	Tone Aksnes	PhD candidate	Norway	Mycobacteria and HIV
Lien	Egil	Professor II	Norway	Lindholm
Håvard	Takle	PhD candidate	Norway	Regeneration
Louet	Claire	Staff engineer	France	Support group
Ma	Qianli	Postdoctor	China	Bone disease
Marstad	Anne	Staff engineer	Norway	Support group
Mediaas	Sindre Dahl	PhD candidate	Norway	Mycobacteria and HIV

Meås	Hany Zakaria	Postdoctor	Egypt	Mycobacteria and HIV
Moen	Siv	Researcher	Norway	Bone disease
Moen	Ingrid Nyhus	PhD candidate	Norway	Inflammation
Mollnes	Tom Eirik	Professor II	Norway	Inflammation
Nedal	Tonje	PhD candidate	Norway	Bone disease
Nilsen	Nadra	Researcher	Norway	Inflammation
Nilsen	Kaja Elisabeth	PhD candidate	Norway	Inflammation
Niynzima	Nathalie	Postdoctor	Norway	Inflammation
Nonstad	Unni	Staff engineer	Norway	Support group
Ostrop	Jenny	Postdoctor	Germany	Regeneration
Oudhoff	Menno	Postdoctor	Netherlands	Regeneration
Parmar	Naveen	Postdoctor	India	Regeneration
Pettersen	Kristine	Postdoctor	Norway	Autophagy
Pinto	Sneha Maria	Postdoctor	India	Systems inflammation
Rodrigues	Eugenia	Postdoctor	Spain	Mycobacteria and HIV
Rokstad	Anne Mari	Researcher	Norway	Inflammation
Ryan	Liv	Staff engineer	Norway	Support group
Sandvik	Arne	Professor	Norway	IBD
Serra	Ignacio Catalan	Postdoctor	Spain	IBD
Silva	Gabriela Brettas	PhD candidate	Brazil	Pregnancy
Skjesol	Astrid	Researcher	Norway	Support group
Spanjers	Roos	Staff engineer	Netherlands	Regeneration
Sporsheim	Bjørnar	Staff engineer	Norway	Support group
Standal	Therese	Professor	Norway	Bone disease
Starheim	Kristian K.	Researcher	Norway	Inflammation
Steigedal	Magnus	Researcher	Norway	Mycobacteria and HIV
Steinkjer	Bjørg	Staff engineer	Norway	Support group
Stenmark	Harald	Professor II	Norway	Inflammation
Stenvik	Jørgen	Researcher	Norway	Inflammation
Strand	Trine Aakvik	Head of administration/ Staff engineer	Norway	Support group
Subbannayya	Yashwanth	Postdoctor	India	Systems inflammation
Sundan	Anders	Professor	Norway	Inflammation
Sætra	Ragnhild	PhD candidate	Norway	Mycobacteria and HIV
Tande	Erlend	PhD candidate	Norway	Inflammation
Ullmann	Sindre	PhD candidate	Norway	Mycobacteria and HIV
Underhill	David	Professor II	USA	
Vik	Randi	Staff engineer	Norway	Support group
Vornewald	Pia	PhD candidate	Germany	Regeneration
Westrin	Marita	Postdoctor	Norway	Bone disease
Wolowczyk	Camilla	PhD candidate	Norway	Autophagy
Yurchenko	Mariia	Researcher	Ucraine	Inflammation
Zwiggelaar	Rosalie	PhD candidate	Netherlands	Regeneration

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FUNDING AND EXPENDITURES 2019

Funding (1000 NOK)	2019
NTNU	23 815
Research Council of Norway (RCN) – Centre of Excellence grant	13 200
Other RCN funding	15 785
Other public funding	14 594
Other private funding	5 513
International funding	1 674
Total funding	**74 581**

Expenditures (1000 NOK)	2019
Personnel and indirect costs	55 191
Equipment	118
Other operating costs	19 272
Total expenditures	**74 581**

Photo:
Page 3, 4, 6, 8, 10, 12: Geir Mogen
Page 14: Kjartan W. Egeberg, Trine A. Strand
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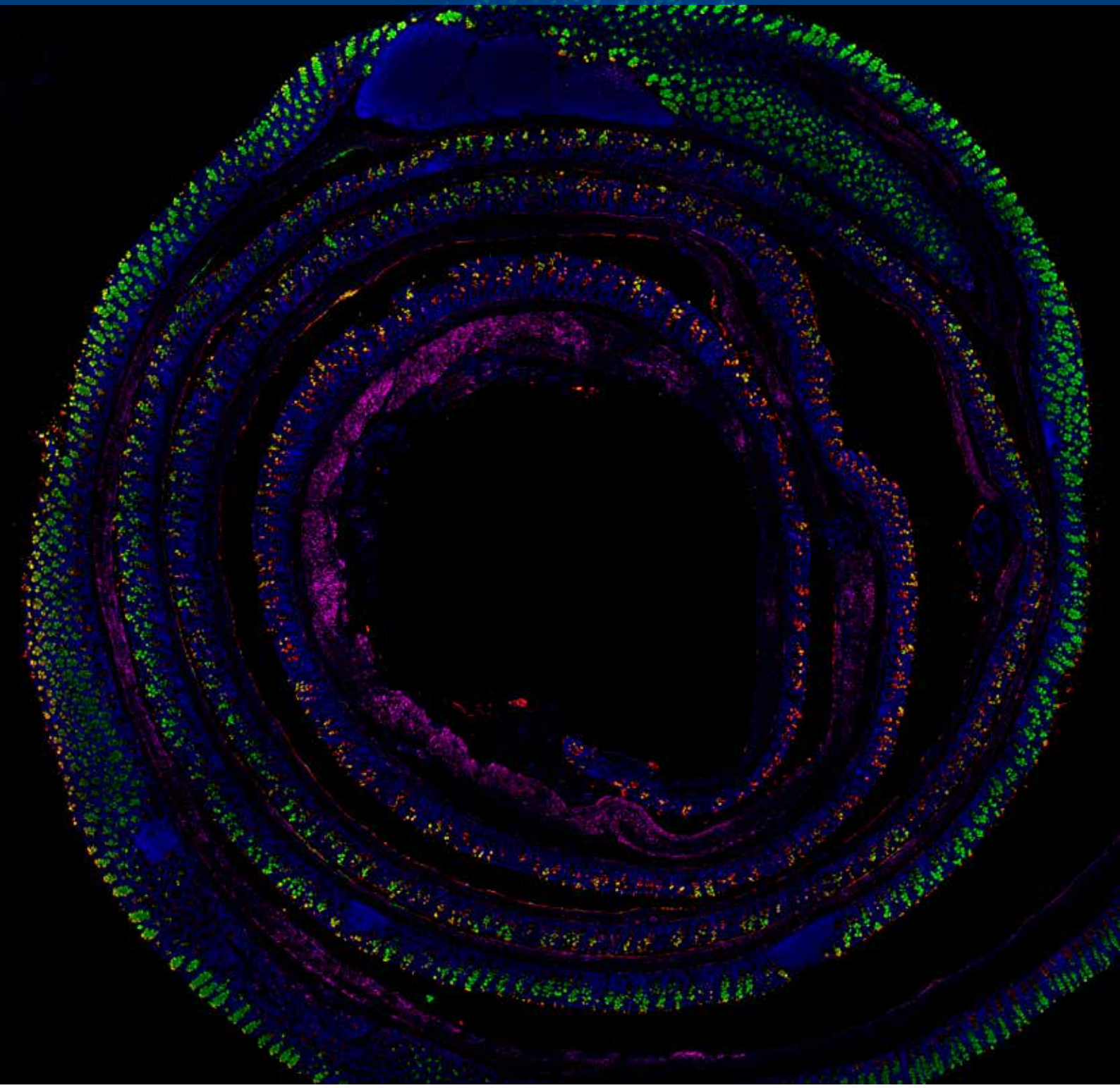
Page 16, 20: Håvard T. Lindholm
Page 17: Kjartan W. Egeberg
Page 18: Kristine Misund
Page 19: Jacob S. Jensen
Page 21, 28: Private/CEMIR
Page 22: Terje Espevik, Trine A. Strand
Page 25: Kjartan W. Egeberg, Adresseavisa
Page 27: St. Olavs hospital
Page 29, 33: Geir Otto Johansen

Photo page 42.
The spiral symbols how research is built layer-on-layer and the outlook zoom into the -black unknown-. A transversal cut of a colon, wrapped in a Swiss Roll (is a way to prepare the samples to have a view of the whole portion of the intestine, in this case, large intestine). And it was stained for a muscle marker (magenta), mature goblet cells marker (green) and secretory cells (red). And the nuclei in blue. By Mara Martin Alonso.



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