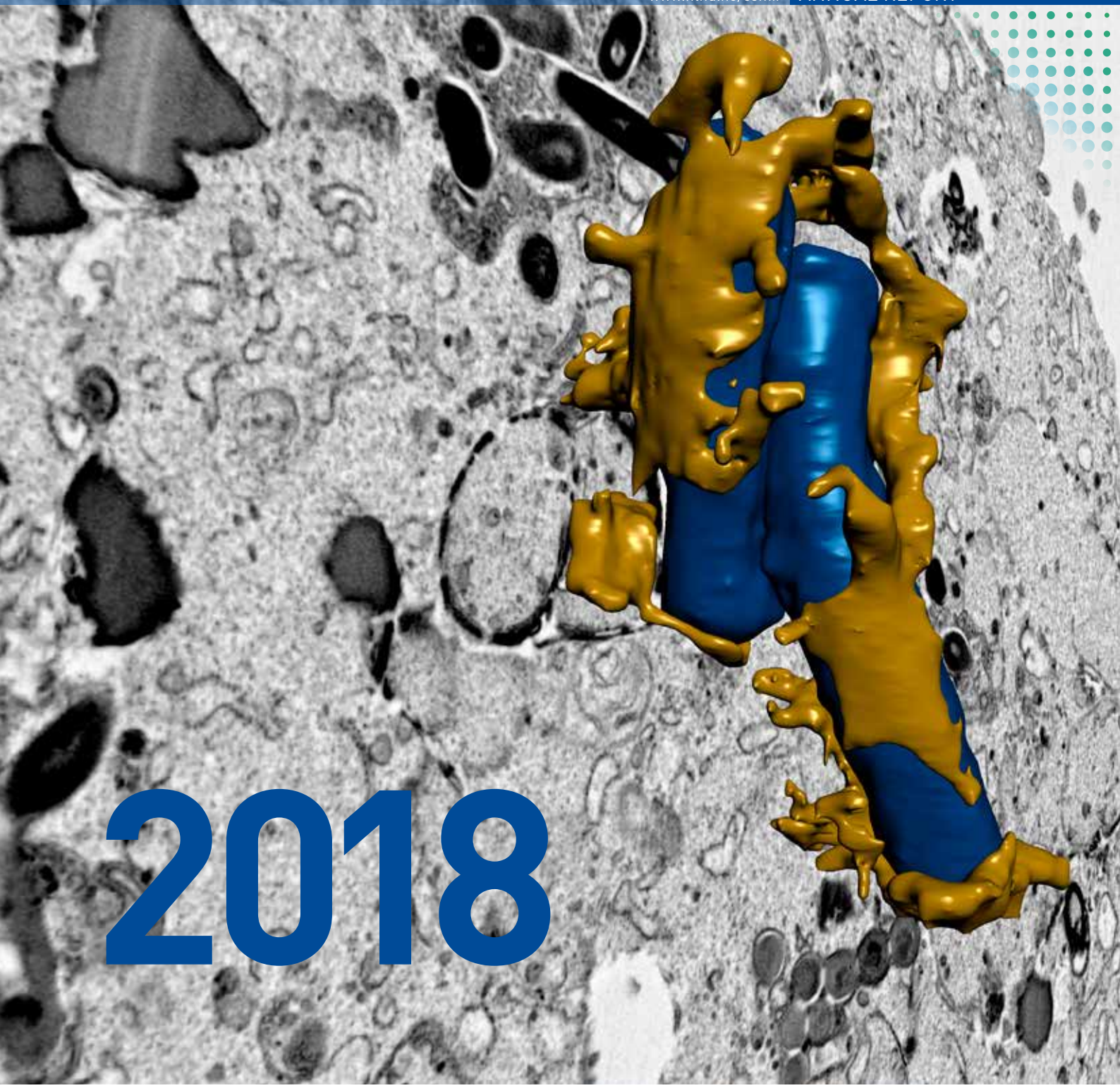
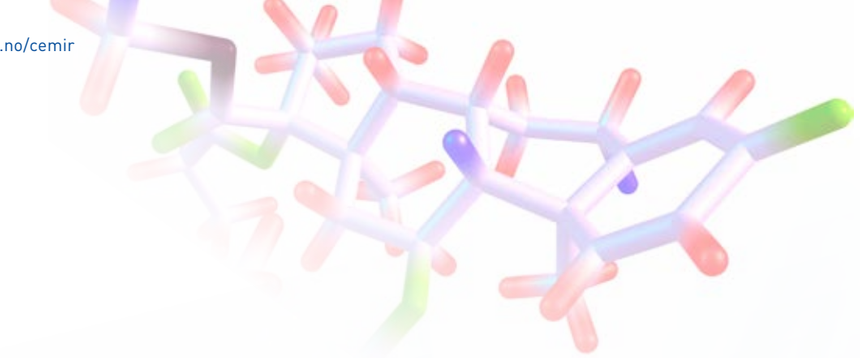


2018

Norwegian Centre of Excellence
The Research Council of Norway

CEMIR
Centre of Molecular Inflammation Research



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Cover photo:
Mycobacterium tuberculosis escapes into the cytosol of a macrophage and is attacked by host autophagic membranes.
3D electron microscopy (FIB-SEM) image taken by Marianne S. Beckwith and Sindre Ullmann.

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 Norwegian Research Council. The committee also visited the Centre in June, 2017. CEMIR received a brilliant evaluation and based on this, the Research Council decided to continue the funding for the last 5 years.

CEMIR has grown to be a vibrant and dynamic center with 67 scientific staff members, 13 engineers, 17 students and one administrative coordinator. In 2017, CEMIR formally became a research unit in the newly established Department of Clinical and Molecular medicine in 2017. This secures the process towards a continuation of the center when the NRC funding ends in 2022.

CEMIR has an active post doc group that in 2017 established their own forum – the PDF forum. They focus on how to develop their own career. The leader of the forum has direct dialogs with the center leader group.

Every month CEMIR members meet at the Journal Club. From 2018 the Journal Club has been organized by CEMIR postdocs. A small group of scientists with different areas of research is selected to present a paper, followed by scientific discussions. The purpose of the Journal Club is to share new relevant scientific work and encourage collaboration between the groups. The Journal Club has been a great success as it has sparked good discussions and engagement.

The CEMIR annual internal seminar was organized in November 2018. The internal seminar is an arena for presentations and discussions on ongoing and future research within the 5 research themes of CEMIR. More than 65 CEMIR members attended the seminar and many of them contributed with presentations followed by scientific discussions. After the seminar we met for dinner and a nice evening at the restaurant NordØst.

The scientific activities at CEMIR have proceeded with very good progress. In 2018 60 papers have been published. CEMIR researchers have published more than 327 articles since 2013, several in high quality journals like Nature, Nature Immunology, Autophagy, PNAS, Plos Pathogens, Cell, Science and J Cell Biol. 26 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. It will be a priority for the centre to further strengthen the collaboration with clinical departments at St. Olavs Hospital. This will help us in achieving the primary goal to identify new therapeutic targets and diagnostic tools for inflammatory diseases.

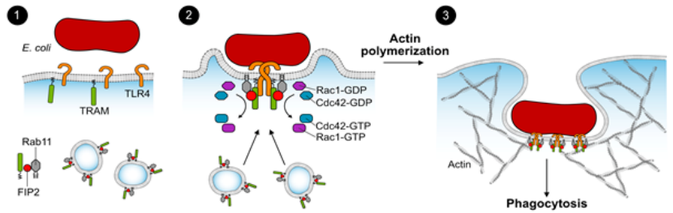
Terje Espevik

Terje Espevik
Centre director

CEMIR RESEARCH THEMES

Theme 1: Intracellular trafficking and compartmentalized signalling

Theme Manager: Professor Terje Espevik



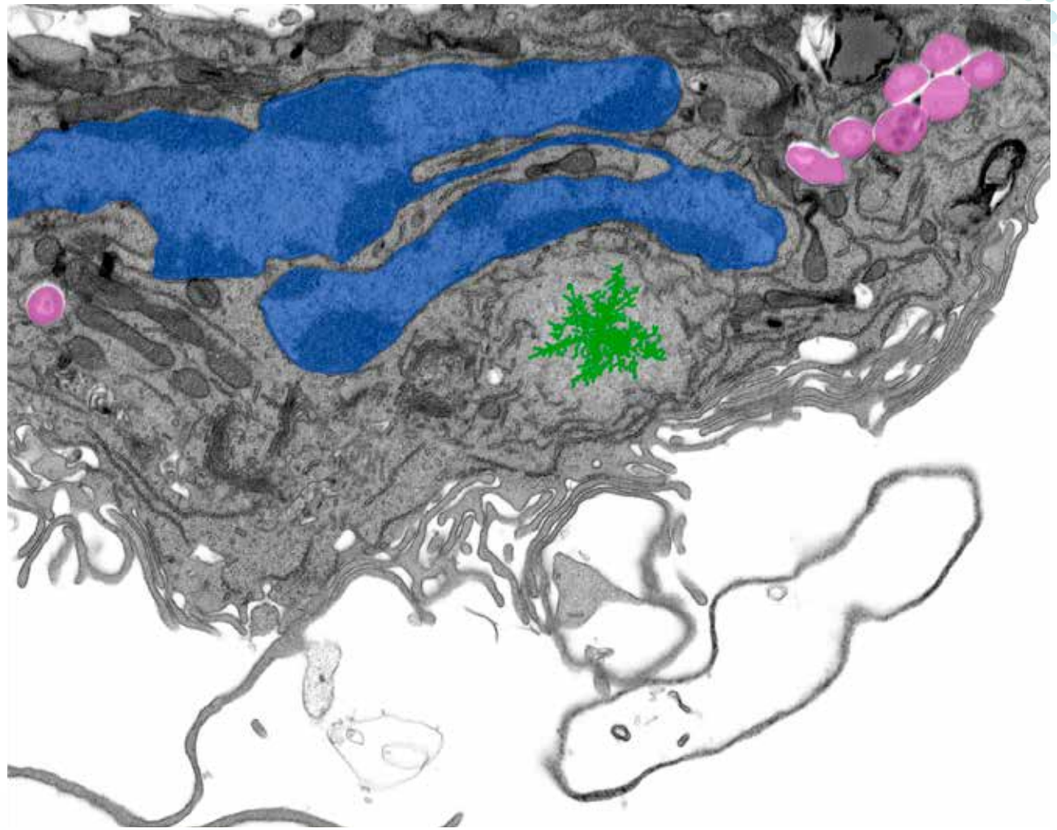
Schematic presentation of our model describing that the TLR4 adapter TRAM is a critical regulator of phagocytosis. TRAM interacts with Rab11-FIP2 which stimulates actin polymerization by activating the Rho-GTPases (Rac1 and Cdc42).

Intracellular trafficking and compartmentalized signalling
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 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. 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 2018
In 2018 we completed and published a comprehensive study describing that SLAMF1 is required for TLR4-mediated signaling and for killing of Gram-negative bacteria by human macrophages. SLAMF1 is present in the endocytic recycling compartment and transports the TRAM adapter to *E. coli* phagosome for TLR4 signaling.

We found that SLAMF1 protein interacts with TRAM and we defined key interaction domains in both proteins. These data suggest that SLAMF1 is a new target for modulation of TLR4–TRAM–TRIF inflammatory signaling in human cells. In 2018 we have initiated a project to construct peptides that interfere with SLAMF1-TRAM interaction and test them for anti-inflammatory effects in various cell systems. We are currently studying how TRAM regulates phagocytosis of *E. coli*. We find that TRAM forms a complex with Rab11 family interacting protein 2 (FIP2) that is recruited to the phagocytic cups of *E. coli*.

In a previous study published last year we show that *M. avium* degraded in lysosomes engage TLR7/8 and elicit inflammatory signaling, whereas a fraction of the mycobacteria manages to establish a compartment where they can replicate undetected (Gidon et al, PLOs Pathogens 2017). We are currently investigating how antibiotic treatment impacts on compartment trafficking and inflammatory responses during established *M. avium* infections. An international collaboration funded by the Olav Thon Foundation was established to characterize the compartments facilitating or inhibiting mycobacterial growth using proteomic approaches. *M. tuberculosis* can rupture host membranes, and we have established a correlative approach using live single-cell imaging and high-resolution 3D electron microscopy to study membrane integrity in relation to inflammatory signaling and cell death. PhD candidates Signe E. Åsberg and Marianne S. Beckwith completed their PhDs on this theme in 2018 and will continue as post docs at CEMIR or the EMBL in Heidelberg, respectively.



In situ NLRP3 inflammasome formation (ASC speck) in Mycobacterium tuberculosis infected macrophage (green ASC speck, pink Mtb, blue nucleus). Image by Marianne S. Beckwith

Major achievements 2018
- Published that SLAMF1 is required for TLR4-mediated signaling in human macrophages (Yurchenko et al., J Cell Biol. 2018)
- Constructed cell-penetrating peptides to inhibit SLAMF1-TRAM interaction
- Discovered that TRAM is instrumental for phagocytosis of *E. coli*
- Discovered that *M. avium* is trafficked to lysosomes upon antibiotic treatment without eliciting inflammatory responses
- Completed 2 PhDs

Ambitions for 2019
- Define the mechanisms involved in TRAM regulation of phagocytosis
- Develop and optimize synthetic peptides that inhibits SLAMF1-TRAM interaction in cell-free assays
- Functional testing of peptides targeting SLAMF1-TRAM interaction in human monocytes and in whole blood
- Generate a panel of knockout THP-1 sublines (CRISPR/Cas9 approach) for more detailed analysis of regulation of phagocytosis and bacterial killing
- Establish the pipeline to retrieve proteomes of mycobacterial phagosomes supporting or preventing growth
- Complete studies on antibiotic impact on *M. avium* trafficking in host macrophages
- Elucidate membrane dynamics and killing of host macrophages by *M. tuberculosis*

Theme 2: Molecular mechanisms of infection and inflammation

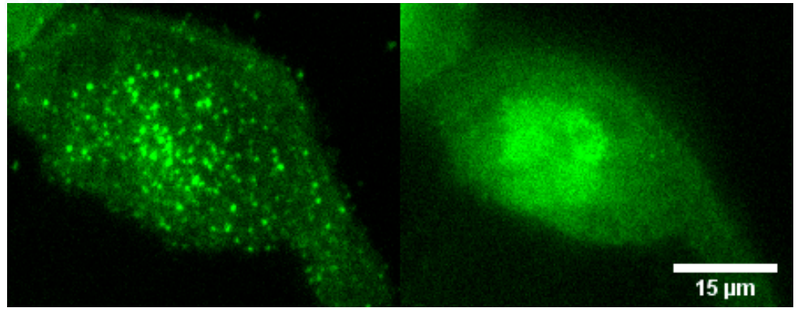
Theme Manager: Professor Trude Helen Flo

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

- In theme 2 we seek to understand infection mechanisms by studying both the pathogens and the host. In 2018 we have made progress in understanding of mycobacterial infections. From the bacterium we have discovered how ***Mycobacterium avium*** changes genetically over the course of infection in individual humans and we have identified unique virulence genes by passing a transposon mutant library through mice. In the host we discovered that non-infected bystander macrophages are activated during ***M. avium*** infection, and work is in progress to elucidate how cell-cell communication is driving anti-mycobacterial host defences. Antimicrobial resistance is becoming a serious concern for treating mycobacterial infections, and in 2018 we have extended our international collaborations to screen for new drugs to ***M. tuberculosis***.
- Another activity in the theme is the investigation of how secretion systems, that are critical bacterial virulence factors, interact with innate immunity and inflammasomes. Yersinia secretion system effector YopJ blocks TAK1 and IKK kinases. We have found that this blockade is sensed as pathological by the host and triggers a novel RIPK1/caspase-8 dependent activation of Gasdermin D and cell death with aspects of both apoptosis and pyroptosis. ***M. tuberculosis*** expresses a secretion system that disrupts host cell membranes and we are elucidating how this leads to inflammasome activation and pyroptosis.
- In Theme 2 we also use the intestinal system as a working model to study development, infection and immunity, and tumorigenesis. We use mouse disease models complemented by ***ex vivo*** organoid models to provide mechanistic insight. We have set up a ***Citrobacter rodentium*** infection model; this mouse model is used to mimic human enteropathogenic and enterohemorrhagic ***E. coli*** infections. We have started infecting our different mouse strains with some preliminary encouraging results.
- Molecular mechanisms of host defences against infection are also important in theme 2. TLR8 recognizes single-stranded RNA. We have continued studies on the significance of this interaction in defences to Gram-positive bacteria and we have discovered that T-cells respond to endosomal HIV via activation of TLR8. We are also in progress of validating a CRISPR/Cas9 knockout screen on HIV-infected T-cells. Some of the target genes facilitate viral growth (host dependency factors) and are followed up with mechanistic studies.
- A continued research focus this year has been epidemiological studies on the risk for bloodstream infections (BSI) and sepsis in the general population. We explored the association between life style, anxiety/depression and iron status with BSI. We have also performed a genome-wide association study in patients with BSI with interesting findings. We have now expanded this cohort by performing studies in the ALL-In population consisting of approximately 70.000 genotypes individuals with 3000 cases with BSI. The activities in BSI and sepsis research have been formalized as a collaboration between NTNU, St Olav's hospital and SINTEF in ***Gemini centre for sepsis research***. We have established a Nordic platform for clinical and translational studies on severe infections and sepsis (financed through NordForsk).

PhD students Nisha Kannan, Hany Meås, Pontus Ørning and Julie Paulsen finished their PhD theses in 2018 and will continue as post docs at Cornell University, CEMIR, the University of Massachusetts, or as clinician at St Olavs Hospital, respectively.



Plasma membrane damage in macrophages infected with Mycobacterium tuberculosis revealed by Total Internal Reflection Fluorescence Microscopy (TIRF) imaging (left). Widefield signal from the same cell shown in the right image. By Ragnhild Sofie Ragnhildstveit Sætra.

Major achievements 2018

- Elucidated how *M. avium* change within humans during infection using serial patient isolates
- Established that *M. tuberculosis* elicits NLRP3 inflammasome activation followed by IL-1ß secretion and cell death by pyroptosis
- Established a *Citrobacter rodentium* infection model in mice
- Discovered how *Yersinia pestis* triggers caspase-8-dependent cleavage of GSDMD and cell death (Orning P. et al., Science. 362(6418):1064-1069)
- Established that TLR8 is a major sensor of several species of pyogenic bacteria in human monocytes and blood
- Established a role for TLR8 in T-cell responses to endosomal HIV
- Identification of critical nodes of viral modulation through an integrated network analysis of host-virus interaction landscape (Bøsl K. et al, BiorXiv)
- Established a mass-spectrometry based proteomics platform for quantitative profiling of protein expression dynamics and post-translational modifications in innate immunity.
- Demonstrated that photochemical internalization holds potential to improve peptide antigen vaccines. (Haug M. et al, Front Immunol. 2018:9:650)
- Showed an association of severe iron deficiency with the risk of bloodstream infections in the prospective population-based HUNT Study in Norway. (Mohus RM. et al. Intensive Care Med. 44:1276-1283).
- Discovered that anxiety and depression symptoms in a general population increase future risk of bloodstream infection in the HUNT Study. (Askim Å. et al. Psychosom Med. 80:673-679)
- Demonstrated that a common variant at the T-cell receptor/ locus protects against gram-positive bloodstream infection in a genome-wide association study in two Norwegian population-based cohorts
- Performed a mendelian randomization study showing a genetic association of body mass index with risk of dying from a bloodstream infection
- Secured grants from the Marie Skłodowska-Curie action, the Olav Thon Foundation, the Research Council of Norway FRIPRO program and NTNU
- Completed 4 PhD students

Ambitions for 2019

- Initiate studies on combined antibiotic and host-directed therapeutic approaches targeting *M. avium* infection in macrophages
- Establish mechanisms and impact of bystander cell activation during *M. avium* infection
- Complete and publish studies on *M. avium* in-patient variation and virulence genes
- Characterize putative inhibitors of the mycobacterial type VII secretion systems with potential anti-mycobacterial properties
- Establish screens for mycobacterial proteins that influence host processes
- Validate CRISPR/Cas9 screens for identification of novel host factors of HIV and Influenza A virus and functionally characterize candidate genes
- Characterize novel regulators of caspase-8 and caspase-1 cell death pathways
- Identify roles of Gasdermin D in host responses to bacterial secretion systems
- Establish the mechanistic basis for a novel negative regulator of type I IFN signalling using in vivo mouse models
- Set up and establish a Helminth infection model in mice
- Finalize the first manuscript regarding the control of infection by epithelial cells as modulators of immune signalling
- Clarify how TLRs inhibit TLR8-IRF5 signalling via a mechanism involving IRAK-1 modifications
- Determine the mechanisms of how Group B Streptococci and *S. aureus* trigger monocyte cell death
- Replicate our findings candidate gene polymorphisms from our GWAS-studies in other cohorts of patients with sepsis and BSI.
- Explore the functional role of candidate gene polymorphism from our GWAS-studies.
- Start a prospective clinical study of patients with septic shock in the intensive care unit with sampling of biological material for genetic, transcriptomic and metabolomic analyses.

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 are 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 will be 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.

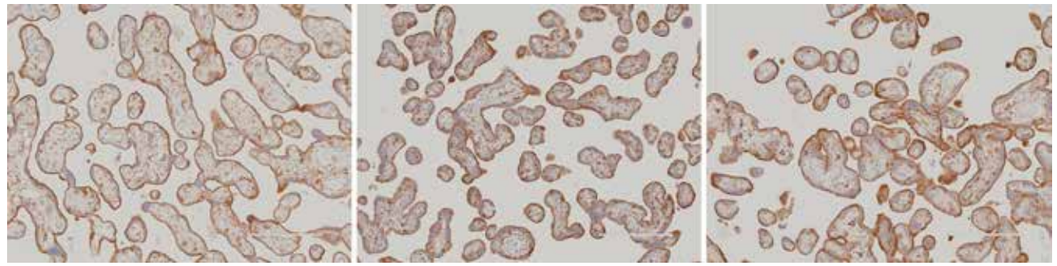
Main activities 2018

CC are very potent activators of the extracellular complement system. In 2018 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 in monocytes and macrophages participates in NLRP3 activation upon phagocytosis of CC. Studies performed in 2018 have demonstrated that CC are active contributors in atherothrombosis through a complement-coagulation dependent induction of monocytic tissue factor (TF). Inhibiting CC-induced inflammation is an important treatment strategy for atherosclerosis. We have continued the work on cyclodextrin effects on CC both regarding solubilization and inhibition of complement activation. Another aspect of studies in 2018 has been on CD5L which is a scavenger-like molecule that participates in the development of atherosclerosis. We found that CD5L regulates important inflammatory responses in macrophages through lipidome remodeling and regulation of the transcription factor RORα. A PhD candidate, Neda Nejati Moharrami, completed her thesis on CD5L functions in 2018.

PRR activation is strongly associated to placental dysfunction at the two sites of maternal-fetal interaction; the fetal cell layer covering the placenta and directly interacting with maternal blood, and the uterine wall decidual tissue. Direct maternal-fetal cellular communication and atherotic lesions with foam cells are being defined in the uterine wall. Inflammasome NLRP3 and cholesterol accumulation, HMGB1 activation of TLR4, and expression and function of other PRRs are being investigated in both the maternal and fetal portion of the placenta. Metabolomic profiling is being further developed for causal classification of the placental disease component of preeclampsia and fetal growth restriction. 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 a cohort of normal and preeclamptic women from 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.

(a) *(b)* *(c)*



Images of FMS-like tyrosine kinase-1 (Flt-1) expression in third trimester placenta in (a) a normal pregnancy at gestational age 38 weeks; (b) a preeclamptic pregnancy without FGR at gestational age 35 weeks; and (c) a preeclamptic pregnancy with FGR at gestational age 33 weeks are shown. Placental tissue was obtained after C-section. Scale bar 100 µM. Photo: Johanne J. Rakner.

Major achievements 2018

- Discovered the role of endogenous CD5L in defining the inflammatory state of human macrophages through remodeling of their intracellular lipidome. Identified RORα nuclear receptor transcription factor as a candidate sensor of CD5L induced changes in intracellular lipid content (Moharrami NN et al., J Immunol, under revision)
- Characterized the scope of inflammatory responses requiring RORα transcriptional activity (Moharrami NN et al., PLoS ONE 2018)
- Published a study describing the effect of IL-6 inhibition on the cytokine network in patients with myocardial infarction (Kleveland, Damås et al., Int J Cardiol 2018)
- Discovered the involvement of cholesterol crystal-induced NLRP3 inflammasome activation in fetal trophoblasts covering the placenta in placental inflammation in preeclampsia (Stødle et al., Clin. Exp. Immunol. 2018)
- Revealed a role for the HMGB1-TLR4 pathway in placental inflammation (Tangerås/Silva et al., Placenta 2018)
- Identified that gestational hypertension in pregnancy is associated with increased risk for subsequent maternal cardiovascular disease in a large epidemiological study combining three Norwegian health registries (Riise et al., J. Am. Heart Assoc. 2018)
- Completed the Inflammation in Obesity Biobank for translational inflammation studies
- Investigated the maternal gestational inflammatory cytokine profile in normal and complicated pregnancies

Ambitions for 2019

- Define the intracellular complosome signals regulating inflammatory responses
- Explore the role of complement in CC-induced atherothrombosis
- Study molecular mechanisms for cyclodextrin effects in human materials to support the use of cyclodextrin as a CC targeting drug against atherosclerosis
- Define the impact of CD5L driven regulation of RORα activity on uptake of extracellular lipids that drive transformation of macrophages into atherogenic foam cells
- Determine how extracellular CD5L controls activation of the complement
- Explore the regulation of PRR mediated danger response and oxidative stress response at the maternal-fetal interface in preeclampsia and fetal growth restriction
- Perform an extensive profiling of the maternal systemic immune status during pregnancy by measuring serum cytokines in normal and complicated pregnancies
- Finalize novel automated image-based immunohistochemistry quantification methods for placental and decidual tissues
- Complete causal classification of placental dysfunction in preeclampsia and fetal growth restriction by metabolomic profiling
- Expanded collection of patient-based biobanks for translational inflammation studies
- Identify shared risk genes and risk traits for preeclampsia and cardiovascular events and mortality in HUNT and CONOR

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

Theme Manager: Professor Arne Sandvik

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

Main activities in 2018

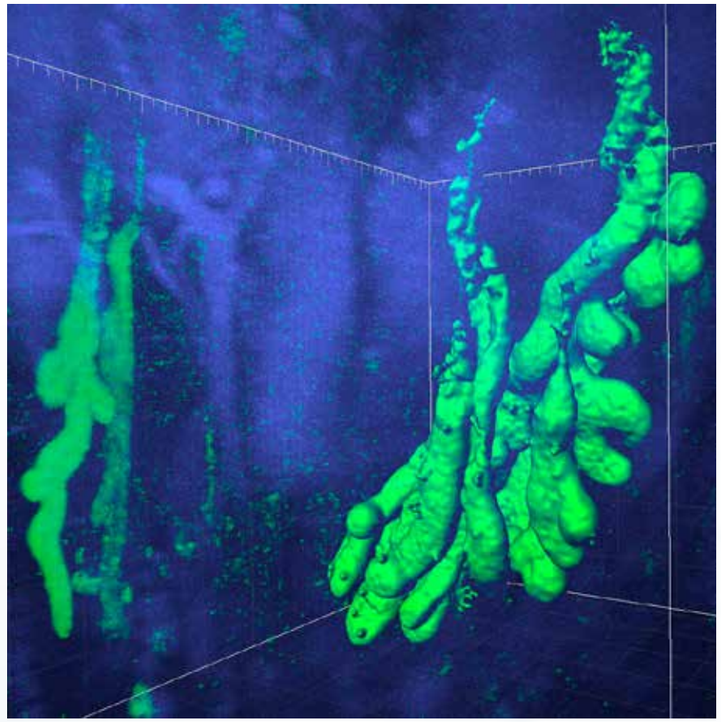
The theme has mainly strived to examine colonic epithelial responses to immunological and physiological signals such as cytokines, chemokines and hypoxia. This work is being done in a collection of patient-derived colonoids which emerges as a very promising model for detailed studies on the role of epithelium in IBD. 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 have started aiming 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 lymphocytes (Singapore collaboration), with laboratory studies ongoing at the different sites from autumn 2018 and two postdocs from the group having visited these.

Main achievements in 2018

- Our planned activities with collaborators at Yale and in Singapore are initiated, and studies ongoing on IBD patient material.
- A major study on the regulation/role of ISG15 in IBD has been completed, and studies on chemokine regulation in organoid models have generated large datasets that are being analyzed.
- More detailed studies on the regulation and role of LCN2/NGAL have been carried out using patient material and colonoids, delineating a likely role for NGAL in proliferation/migration.
- A longitudinal treatment response study has started, aiming to evaluate NGAL and innate lymphocytes as prognosis markers in addition to generating data to understand the heterogeneous response to anti TNF treatment.
- Dr. Mara Martin-Alonso from the Oudhoff Lab was awarded a prestigious Marie Skłodowska-Curie fellowship on her work studying muscle-derived niche factors that are important for intestinal stem cells in homeostasis and disease.

Ambitions for 2019

- Intensify efforts to establish also small intestinal enteroids, for specific studies on Crohn's disease in the small intestine.
- Initiate studies on the precise mechanisms for regulation and molecular function(s) of LCN2/NGAL in the small and the large intestine, during inflammation and wound repair.
- Continue the efforts of integrating gene expression results from IBD biopsies and epithelial microdissectates with genetic variation.
- Delineate IBD-relevant immunological mechanisms originating in the epithelial cells during normoxia and hypoxia.
- Finish collaborative work on Setd7 and the Wnt pathway, and the studies on Lsd1 and Mmp17 in intestinal inflammation and regeneration.



Cleared tissue from intestinal biopsy in Crohn's disease, showing (in 3D) ulcer-associated cell lineage glands with buds and neutrophil granulocytes positive (green) for Neutrophil Gelatinase-Associated Lipocalin. Photo: Bjørnar Sporsheim/Atle van Beelen Granlund

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

Theme Manager: Professor Therese Standal

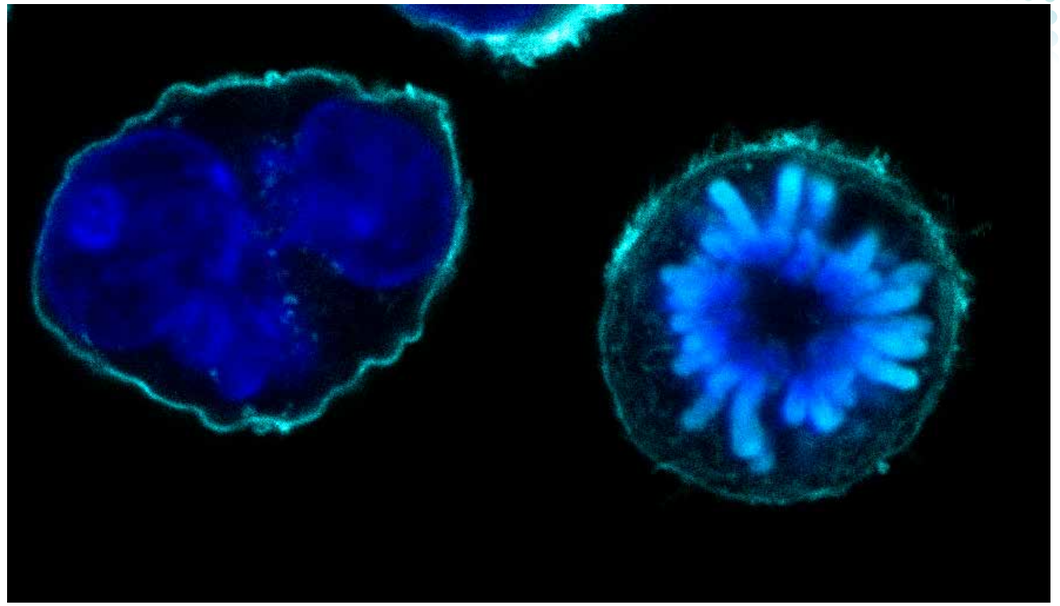
Cancer cells modulate the tumor microenvironment by secreting factors that promote chronic inflammation, inhibit immune surveillance and disrupt bone homeostasis. Pattern-recognition receptors (PRR)s are signalling immune-receptors that mediate inflammatory responses. These receptors sense pathogen or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

Main activities in 2018

In 2018 we studied the role of IL-6 for cancer cachexia. We found that blood samples from cancer patients contain autophagy-inducing bioactivities and that this activity associated with loss in body weight. The effect may be mediated by IL-6 secreted from cancer cells and complexed to soluble IL-6 receptor to induce responses in muscle cells. We also studied if immune reactions within solid tumors is controlled by autophagy by using a breast cancer metastasis model in immunocompetent mice (4T1) and by combining RNA sequencing data from the model with in silico data mining of patient data. The importance of autophagy in multiple myeloma was also studied, in particular in relation to how the cancer cells handle large amounts of immunoglobulin protein. We further continued our studies on the role of IL-32 in multiple myeloma disease progression, this year focusing mainly on the role of IL-32 for cancer cell survival. We have also performed glycoproteomics of serum from a large set of myeloma patients samples and found that immunoglobulins from patients with bone disease are differently glycosylated compared with patients without bone disease. We are now investigating the importance of immunoglobulin glycosylation for bone loss in a myeloma mouse model. Additional studies have focused on the role of PRRs in the tumor microenvironment. We have observed altered PRR expression and signalling in tumor cells which may drive inflammatory responses that support metastasis. The signalling pathways and responses induced in these cells in response to PRR activators is currently being investigated. Cancer cells have also been found to secrete PRR activating components that induce inflammatory responses in PRR-expressing cells in the tumor microenvironment and we are currently focused on identifying the nature of these components. We also aim to identify which cells are activated by these components and how this affects cancer cell survival.

Major achievements in 2018

- Finished a manuscript that define a discrete breast cancer specific oxidative stress gene-expression response with clear prognostic value.
- Submitted a manuscript that describes the control of IL-6 secretion from cancer cells and the possible implications for cancer cachexia.
- Identified an immune cell population that is unique in a model of aggressive solid tumors and identified the cancer cell derived chemokine that recruit these cells in vitro.
- Developed and performed screens in primary macrophages of novel CSF1R inhibitors designed at NTNU and an international partner.
- Established a novel approach for CRISPR CAS9 mediated gene editing without use of plasmid or virus carriers.
- Submitted a manuscript demonstrating that BMP4 gene therapy in mice inhibits myeloma tumor growth, but has a negative impact on bone.
- Identified glycosylation changes in immunoglobulins obtained from patients with multiple myeloma, and how such changes may impact bone health in these patients.
- Characterized the role of IL-32 for myeloma cell survival in vitro and in vivo.
- Determined how IAP-agonists trigger inflammatory cell death in osteoclasts
- Described a novel regulator of RIPK1-driven inflammation and cell death in macrophages
- Discovered how inflammatory cell death can synergize with DNA-damage in multiple myeloma cells.



Malignant plasma cells stained for phosphorylated histone 3. Image by Kristin Roseth Aass.

Ambitions for 2019

- Explore IPR protection and publish the oxidative stress gene-expression signature in primary biopsies as an additional tool for guiding breast cancer treatment
- Publish our finding that secretion of particular BMP antagonists control breast cancer development
- Evaluate tumor development and immune cell infiltrate after disrupting genes encoding specific chemokines and autophagy proteins in the cancer cells
- Find how autophagy may control IFN responses in tumors
- Describe if and how IL-6 trans-signaling induce autophagy in cardiomyocytes and skeletal muscle
- Find how intracellular protein aggregates is released from myeloma cells, investigate their possible pathophysiological role and determine if other cell types can do the same
- Establish a mouse breast cancer model that allow intra-tumor imaging of innate immune cells infiltrating solid tumors
- Publish our data on the role of immunoglobulin glycosylation for bone loss in multiple myeloma.
- Submit a paper on the role of IL-32 for myeloma cell survival.
- Determine the consequence of altered PRR expression in cancer cells and how this affects survival, migration and invasion of cancer cells.
- Identify PRR-activating components released from cancer cells and determine which cells are activated by these components and how this affects survival.
- Publish findings on IAP-agonists in osteoclasts.
- Further describe the importance of novel RIPK1-regulators.
- Explore the role of inflammatory cell death in multiple myeloma patient samples and mouse models.

LABORATORY FACILITIES

The new Zeiss LSM 880 Airyscan super resolution confocal microscope.

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.

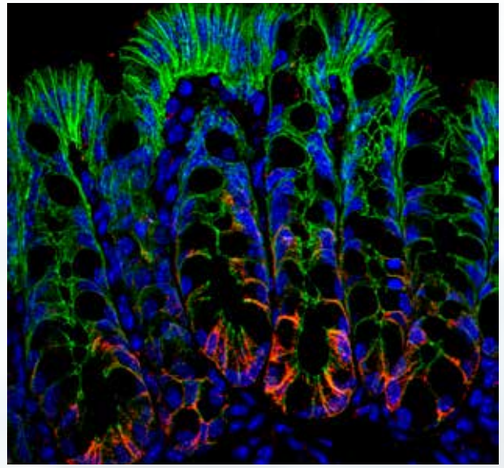
CEMIR-use of the Imaging Core Facility
Researchers and students at CEMIR have access to a multitude of different imaging techniques, for live cell studies as well as imaging of fixed cells and tissue preparations. These instruments are all part of the Cellular and Molecular Imaging Core Facility, CMIC, 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 at 27 fps (480x480). The instrument is otherwise well equipped with an incubator system for controlled temperature and CO2 environment, piezo-controlled sample stage for acquiring high precision and fast z-stacks, high quality optics including a high NA Autocorr 40X W objective for optimal image quality in aqueous medium. It also has a Prime 95B Scientific CMOS camera with a quantum efficiency of 95%, which means extreme sensitivity and high frame rates for fluorescence images, up to 84 fps (1200x1200). Zeiss Zen Connect software can be used to combine and correlate data from other microscopes and modalities, such as electron microscopy for a better understanding of your samples.

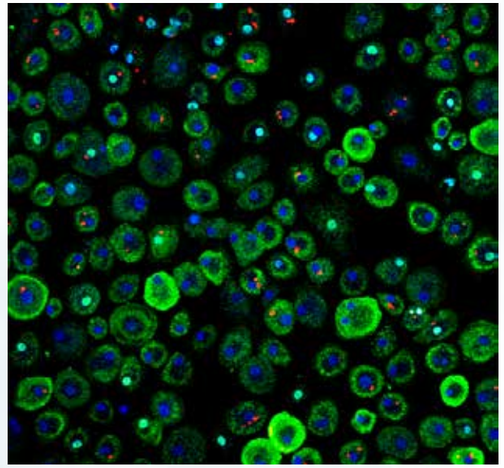
Furthermore, CMIC has a high-end Leica SP8 STED 3X super-resolution microscope with the possibility to perform single molecule detection and analysis that is particularly useful for studying molecular interactions in cells.

In addition, CEMIR researchers are using Focused-Ion Beam Scanning Electron Microscopy (FIB-SEM) in collaboration with the NTNU Nanolab. A new 3-D serial block face scanning electron microscope has also recently been added to the instrument park.

The BSL-3 lab contains an advanced Leica SP8 confocal microscope making it possible to study infections in immune cells.



Picture from the new Zeiss LSM 880 Airyscan super resolution confocal microscope showing b-catenin staining (green) in intestinal epithelial cells and Lrg1 (red) staining concentrated at the bottom of the crypts where stem cells are located. Nuclei stained in blue. 40X magnification picture. Photo taken by Mara Alonso.



Low resolution overview (20x, no digital zoom) of human primary macrophages. Image is a sum projection of a 3d stack. In green is the transcription factor IRF1, in red is Mycobacterium avium, in blue is draq5. Acquired on the Zeiss Airyscan.
Photo taken by Alexandre Gidon.

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 co-inside 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 a immunocompetent mouse model with data mining in large databases of tumour biopsy and clinical information.

Autophagy is also a way to mobilize amino acids and other nutrients during starvation. Such 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 now study how IL-6 secretion is controlled and how muscle cells induce autophagy in response to IL-6.

Autophagy is crucial for removal of intracellular protein aggregates. In myeloma cells, these cancer cells produce high levels of immunoglobulin. A high rate of protein degradation is important in these cancer cells and patients respond to proteasome inhibitors. We study the role of autophagy in myeloma to determine how these cancer cells handle large amount of immunoglobulin protein. Particularly, we investigate the role of protein aggregation and the faith of these aggregates in cell cultures and patients.
The group is also engaged in screens of chemical tyrosine kinase inhibitors designed and synthesized by our collaborators at NTNU. The novel compounds are monitored for effects on macrophages in culture, tumors and tissues.

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 diseases. 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.

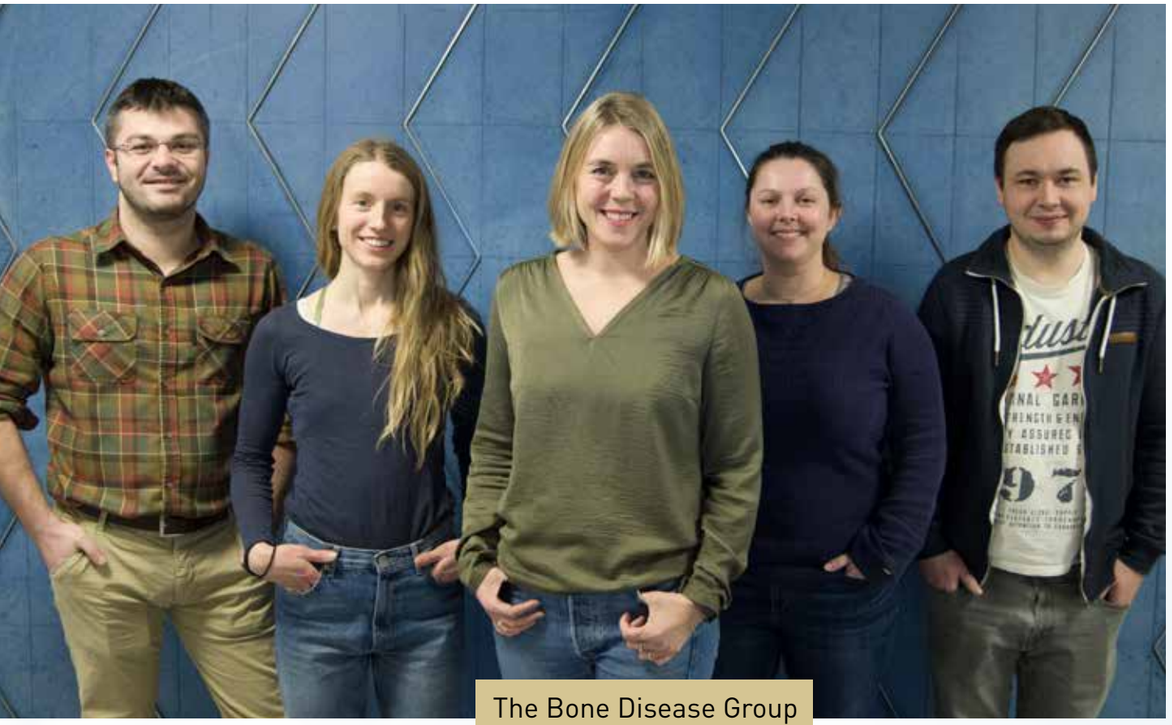
The Research Group is led by Professor Ann-Charlotte Iversen. In 2018, the group counted 9 persons; Professor Iversen, 1 post doc, 3 PhD students, 3 MD PhD students, one MD student. Three MD students completed their MD thesis in the group. In 2019 our group will grow with 2 MD PhD students and 1 staff engineer.

The Inflammatory Bowel Diseases (IBD) Group

The inflammatory bowel diseases (IBD) research group studies disease mechanisms in IBD, with patients and clinical biobanks as central resources. The ultimate aim is to use knowledge of IBD pathobiology to improve diagnostics and prognostics, and for optimization of treatment and drug discovery. The IBD projects concentrate on understanding how mucosal homeostasis is disrupted 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. 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 of elements of the inflammatory pathways.

The IBD group is closely connected with clinical medicine, also through combined university/hospital positions. The group moreover collaborates with clinicians in 7 different hospitals in the Central Norway Health Region, and regional hospital staff is involved in translational research projects. The group 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 (high-throughput genomics and transcriptomics), and is experienced within transcriptome analysis and bioinformatics. The group has access to excellent animal experimental facilities, using e.g. genetically modified mice.

An international network has been established with formal collaborative agreements, and 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

Loss of bone is a common feature of different inflammatory diseases as well as for cancers metastasizing to or located within bone. Multiple myeloma is a cancer of plasma cells, located within the bone marrow. 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. 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 differentiation or activation of bone cells.

We have established protocols for differentiation of bone cells, and have easy access to primary cells from myeloma patients. For in vivo studies we either use a traditional xenograft model allowing engraftment of myeloma cell lines, or a novel human-mouse scaffold model developed in the laboratory of Anton Martens, the Netherlands. This model enables 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 acquirement of a uCT 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 strengthened our opportunities in terms of bone quality assessments.

The group is led by professor Therese Standal and currently consists of two PhD students, one researcher and one technician. Our group profits from a close collaboration with clinicians and researchers at the Center of myeloma research headed by Anders Sundan, NTNU. In close collaboration with the Hematology Department at St. Olavs Hospital, the Regional Biobank and the Nordic Myeloma Study Group we have access to well characterized samples from myeloma patients.

Cellular and Molecular Mechanisms in Regeneration

Tissue repair is an important process that is required to resolve inflammation and/or prevent chronic infection. In addition, prolonged inflammation or aberrant repair can be the initiation of cancerous lesions. We are interested in the cellular and molecular mechanisms that trigger and execute these reparative and regenerative processes. Commonly, there is interplay between various cell types, each giving and receiving cues that together orchestrate an optimal response, to ultimately clear an infection or repair the damage. Furthermore, there are biomechanical cues such as tissue stiffness that can modulate these responses. We use in vivo disease models to study this in the most physiologically relevant manner, and we use in vitro organoid cultures for mechanistic insight. Although our group studies various processes, our common organ of interest is the intestinal system.

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. Drs. Fabio Rossi (UBC, Vancouver) and Colby Zaph (Monash University, Melbourne) are active collaborators on the role of SETD7, and we published a collaborative effort in Cell Stem Cell in 2018. 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 new collaboration with the group of Dr. Kim Jensen (The BRIC, Copenhagen, Denmark) to help comparing foetal and regenerative epithelium. 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 2018 consisted of 4 Postdocs, 2 PhD students, 2 MSc students, and 1 Research Assistant.

Mycobacteria and 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. There has been an increase in TB following the HIV epidemic: HIV increases the risk for active TB and one third of HIV deaths are from TB. Despite the success of anti-retroviral treatment, HIV patients experience low-grade inflammation and increased risk of co-morbidities. 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 three more research scientists, three post docs, three PhD students, one medical research students 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) and H Stenmark (OUS). We also pioneer the use of Focused Ion-Beam Scanning Electron Microscopy at NTNU Nanolab to perform high resolution imaging of intracellular infections. Central external collaborators are P Sikorski (NTNU, physics/nanotech), K Tasken (NCMM UiO, T-cells), AM D Riise & M Trøseid (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 (Linköping University, TB screens).

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.

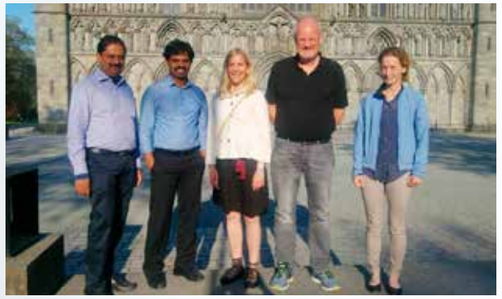
We believe that our basic research-focused systems-level approaches would yield deeper and broader understanding of inflammatory signaling which will have enormous translational potential.

The research group led by Richard K. Kandasamy currently includes 2 Ph.D. students, 4 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), Andre Muller (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).

10 MILLION NOK FROM THE OLAV THON FOUNDATION TO DO RESEARCH ON TUBERCULOSIS

In January 2018 CEMIR Professor Trude Helen Flo received 10 million NOK from the Olav Thon Foundation to do research on tuberculosis. The Olav Thon Foundation awards professional prizes and support for outstanding teaching and research in the fields of medical and mathematical-science. Trude H. Flo and her partners in Sweden, India and Germany will investigate the interaction between the tuberculosis and host cells as well as screening a chemical library of natural compounds for new antibiotics. The aim is to create new therapeutic approaches to face the challenges of increasing antimicrobial resistance in tuberculosis.

The prize was handed over March 8. A scientific seminar was held at the University of Oslo with lectures by all the research award recipients. In the afternoon, the very formal award ceremony was held in the University Aula in Oslo. Maria Lerm, Trude Helen Flo, Olav Thon. Photo: Katrine Lunke/APELAND



A Thon project kick-off meeting was organized May 15–16. Partners Maria Lerm from Linkøping University, Norbert Reiling from Research Center Borstel and Keshav Prasad from Yenepoya University Mangalore came to visit to kick off the Thon project on antimicrobial resistant M. tuberculosis. We will try reveal where in the macrophage Mtb is hiding by performing proteomics on Mtb phagosomes, and new drugs to AMR Mtb by screening infected macrophages with compound libraries.

COOPERATION WITH CLINICAL DEPARTMENTS 2018

The vision of CEMIR is to lay the foundation for new therapeutic targets and diagnostic tools for inflammatory diseases through research in molecular innate immune responses. The inflammatory processes identified and explored at CEMIR may play a role in the pathophysiological process in diseases such as infections, atherosclerosis, preeclampsia, multiple myeloma and inflammatory bowel disease (IBD) and therefore could represent future therapeutic targets in these diseases. As important is to identify new diagnostic and prognostic markers for disease severity and outcome. Accordingly, studies on these clinical aspects of molecular inflammation have been a main topic in CEMIR's research strategy. To achieve this we have established a close collaboration with the clinical departments and CEMIR. CEMIR benefits from a close integration between NTNU and St.Olav's Hospital and the location of both institutions at Øya Campus. Several of our staff members are employed at the hospital and the university.

This close integration between CEMIR and St.Olav's Hospital has also been important in building up several biobanks with clinical specimens from various patient groups. As shown in several papers from 2018, analyses using these clinical materials have demonstrated the clinical relevance of results generated in more experimental systems. In inflammatory bowel disease we have used human peripheral blood mononuclear cells and colonic biopsies in translational studies. In studies of pleeclampsia, we have used syncytium layer of the placenta to study placental inflammation. We have used patient material from multiple myeloma patients and lung cancer patients recruited and with follow-up at St Olavs Hospital to study cancer markers. We have published several sub-studies on clinical materials collected in interventional studies with cytokine inhibitors in patients with myocardial infarction. Finally, we have measured iron status in the population-based HUNT2 study linked with our Mid-Norway Sepsis Register.

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.

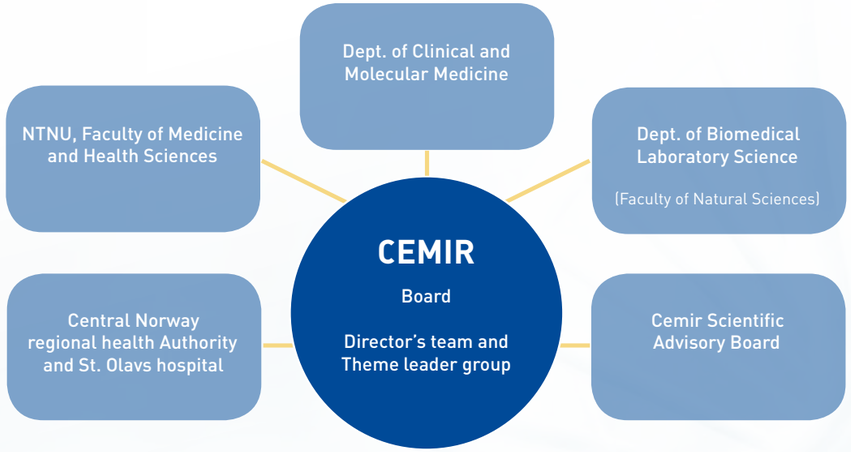
Six outstanding professors from other institutions are affiliated with CEMIR: Kate Fitzgerald and Egil Lien from UMass Boston, David Underhill from Cedars-Sinai LA, Eicke Latz from Univ. Bonn, and Harald Stenmark and Tom Eirik Mollnes from Oslo University Hospital. They work in the fields of cell biology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

ABOUT CEMIR



CEMIR's host department is Department of Clinical and Molecular Medicine at the Faculty of Medicine and Health Sciences, NTNU. Agreement documents regulate the cooperation with our partners. The Centre management reports to the CEMIR board.

From the start in 2013 CEMIR had two main partners that contributed by performing research activity and providing financing: Sør-Trøndelag University College (HiST) and The Central Norway Regional Health Authority/St.Olavs Hospital. From January 2016 NTNU and HiST merged, and the research group from HiST became an internal NTNU collaborator formally hosted by the Department of Biomedical Laboratory Science and the Faculty of Natural Sciences. The fruitful collaboration continues after the merge and the Faculty of Natural Sciences continues to be represented in 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 were held in 2018.

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) has five members:
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. The next SAB meeting will be held June 3, 2019.

COMPLETED PHDs in 2018

for the degree of Philosophiae Doctor

Marianne Sandvold Beckwith
defended her thesis *Targeted correlative light and electron microscopy in the study of host-pathogen interactions* March 21, 2018 at Norwegian University of Science and Technology (NTNU), Center of Molecular Inflammation Research (CEMIR).

The experimental work was conducted at the Department of Clinical and Molecular Medicine at NTNU with Professors Trude Helen Flo and Øyvind Halaas as supervisors.

Nisha Kannan
defended her thesis *Understanding and preventing Mycobacterium avium infections* May 30, 2018 at Norwegian University of Science and Technology (NTNU), Center of Molecular Inflammation Research (CEMIR).

The experimental work was conducted at the Department of Clinical and Molecular Medicine at NTNU with Researcher Magnus Steigedal, Professor Trude Helen Flo and researcher Markus Haug as supervisors.

Julie Paulsen
defended her thesis *Risk and prognosis of bloodstream infections: The influence of obesity and lifestyle, genetic variation, and clinical factors present at the time of infection. The HUNT study and the Nord-Trøndelag Bacteremia registry* May 25, 2018 at Norwegian University of Science and Technology (NTNU), Center of Molecular Inflammation Research (CEMIR).

The experimental work was conducted at the Department of Clinical and Molecular Medicine at NTNU with Professor Jan Kristian Damås, Associate Professor Erik Solligård and Professor Bjørn Olav Åsvold as supervisors.

Hany Zakaria Meås
defended his thesis *HIV infection of CD4+ T cells: New insights into innate sensing and host dependency factors* September 13, 2018 at Norwegian University of Science and Technology (NTNU), Center of Molecular Inflammation Research (CEMIR).

The experimental work was conducted at the Department of Clinical and Molecular Medicine at NTNU with Professor Trude Helen Flo and researcher Markus Haug as supervisors.

Signe Elisabeth Åsberg
defended her thesis *The Drug, the Bug and the Macrophage: Interactions between antibiotics, mycobacteria and macrophages at the single cell and subcellular level* November 9, 2018 at Norwegian University of Science and Technology (NTNU), Center of Molecular Inflammation Research (CEMIR).

The experimental work was conducted at the Department of Clinical and Molecular Medicine at NTNU with Professor Trude Helen Flo, researcher Alexandre Gidon and Professor David Underhill (Cedars-Sinai, LA) as supervisors.

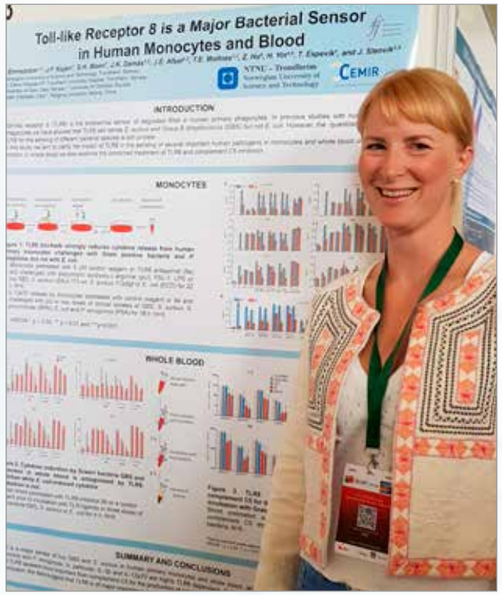
Pontus Ørning
defended his thesis *Host Defense Mechanisms Against Bacterial Secretion Systems – Linking Cell Death to Inflammation* November 27, 2018 at Norwegian University of Science and Technology (NTNU), Center of Molecular Inflammation Research (CEMIR).

The experimental work was conducted at the Department of Clinical and Molecular Medicine at NTNU and University of Massachusetts Medical School with Professor II Egil Lien, CEMIR, NTNU/University of Massachusetts Medical School and Professor Katherine A. Fitzgerald, University of Massachusetts Medical School as supervisors.

Neda Moharrami
defended her thesis *Role of CD5L in control of human innate immune function* December 12th, 2018 at Norwegian University of Science and Technology (NTNU), Center of Molecular Inflammation Research (CEMIR).

The experimental work was conducted at the Department of Clinical and Molecular Medicine at NTNU with Professor Terje Espevik and researcher Victor Boyartchuk as supervisors.

SCIENCE COMMUNICATION AND OUTREACH ACTIVITY



Birgitta Ehrnström presented a poster at the TOLL 2018 conference (Editing Innate Immunity), Portugal June 2018

CEMIR members contributed with more than 60 posters and oral presentations at conferences in 2018, such as

- EMBL conferences/seminars
- TOLL 2018 conference (Editing Innate Immunity)
- 15th International Conference on Innate Immunity
- European Congress of Immunology
- 12th International BMP Conference
- Nordic Proteomics Conference
- 2nd International NTNU Symposium on Current and Future Clinical Biomarkers of Cancer
- Congress of the International Society for the Study of Hypertension in Pregnancy (ISSHP)
- Network of European Bioimage Analysts Conference
- Annual European Congress of Rheumatology (EULAR 2018)
- Royal College of Physicians Annual Conference
- 11th International Conference on Complement Therapeutics
- 13th Congress of ECCO
- Society for Leukocyte Biology/International Endotoxin and Innate Immunity Society conference

In January CEMIR Professor Trude Helen Flo received 10 million NOK from the Olav Thon Foundation, to do research on tuberculosis. Her research project got a lot of attention in the media.

In October Pontus Ørning, Kristian Starheim and Egil Lien from CEMIR published a paper in Science: Pathogen blockade of TAK1 triggers caspase-8–dependent cleavage of gasdermin D and cell death. Gemini and Forskning.no wrote about the publication and the scientific findings.

NTNU-forsker får ti millioner

Professor Trude Helene Flo ble i dag innvilget ti millioner over fire år for å forske på bekjempelse av tuberkulose.

Professor Trude Helene Flo ved NTNU mottar 10 millioner fra Olav Thon Stiftelsen.

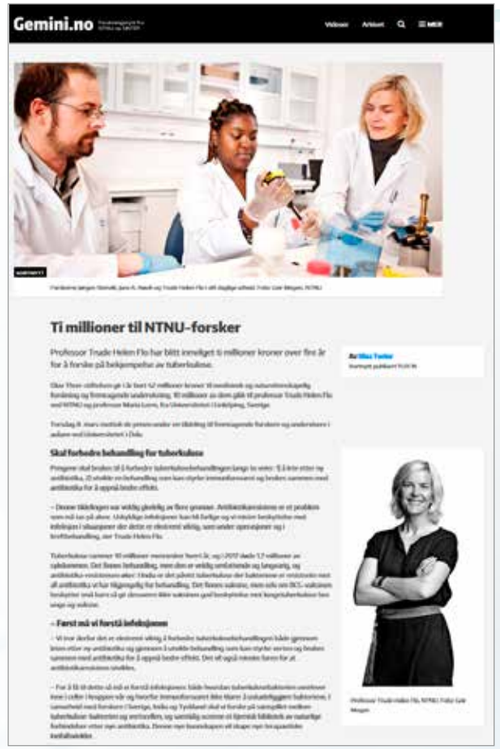
Adresseavisa January 11, 2018

Immunceller sprenger seg selv for å beskytte mot bakterier

Det er travle dager på jobb for immunforsvaret. En liten tanst kan være å vite at det finnes en gjeng dedikerte immunceller som er villig til å eksplodere seg selv, for å gi beskjed til de andre om faren som er på ferde.

GEMINI October 15, 2018

Forskning.no October 27, 2018



Gemini January 11, 2018

CEMIR on TV and radio in 2018:
NRK1 Television April 12, 2018: Viten og Vilje – Fedmekirurgiens bakside. Postdoc Lobke Gierman was interviewed by Per Olav Alvestad about obesity and inflammation.

NRK Radio December 7,2018: God Ettermiddag Trøndelag, Forskerprat. Professor Trude Helen Flo talked about research on Tuberculosis (Journalist Johannes Børstad)

Snapshot of the television serie season 2018 NRK1

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.

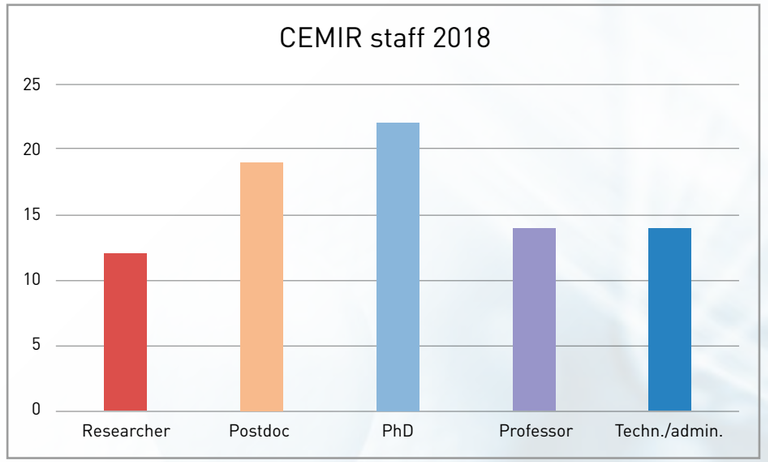
At CEMIR we currently have two innovation strategies for controlling inflammation. The first one is to control inflammation by interfering with the Toll-like receptor 4 signaling pathway. The Espevik group has identified interaction domains in two intracellular proteins that is required to mount an inflammatory response towards Gram-negative bacteria. Based on these data we have constructed peptides that interfere with the interaction of these two proteins. These 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 as an "optimization project" from 2018.

The other innovation strategy is to control inflammation by interfering with the colony stimulating factor 1 receptor (CSF1R). CSF1R is crucial in the differentiation and survival of macrophages. CSF1R is overexpressed in many cancer types and also on tumor-associated macrophages. Thus, chemical inhibitors of CSF1R may be useful in several conditions driven by hyperactive macrophages such as inflammatory diseases and cancers. Organic chemists at NTNU (Hoff/Sundby) have designed and synthesized chemical ATP-competitors that inhibit CSF1R activity with a potency and specificity that is superior to alternative inhibitors in kinase assays. The compounds are screened for ability to interfere with CSF1R induced signaling in macrophages and CSF1R driven cell survival. The best candidates are further tested for administration, distribution, metabolism and excretion (ADME) at the Max-Planck, Lead Discovery Center (LDC) in Dortmund. In parallel, the Bjørkøy group screen novel compounds from LDC in the macrophage signaling assays. The initial aim is to test the novel NTNU-compounds in an animal model of osteoporosis. The Norwegian Research Council supports the project as an "optimization project" from 2019.

CEMIR STAFF 2018

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

By the end of 2018 67 scientific staff members, 14 technicians, 17 students and one administrative coordinator associated with the Centre.



Name		Position	Nationality	Research group
Aas	Kristin	PhD candidate	Norway	Bone disease
Alonso	Mara	Postdoctor	Spain	Regeneration
Andersen	Sonja	Staff engineer	Norway	Autophagy
Bakke	Siril Skaret	Postdoctor	Norway	Inflammation
Beckwith	Kai	Postdoctor	Norway	Mycobacteria & HIV
Beckwith	Marianne Sandvold	PhD candidate	Norway	Mycobacteria & HIV
Bjørkøy	Geir	Professor	Norway	Autophagy
Boyartchuk	Victor	Researcher	Ukraine	Inflammation
Buene	Glenn	Staff engineer	Norway	Bone disease
Bugge	Marit	Postdoctor	Norway	Inflammation
Bözl	Korbinian Michael	PhD candidate	Germany	System Inflammation
Damaas	Jan Kristian	Professor	Norway	Inflammation
Dragset	Marte Singsås	Postdoctor	Norway	Mycobacteria & HIV
Egeberg	Kjartan	Staff engineer	Norway	Inflammation
Ehrnstrøm	Birgitta	PhD candidate	Sweden	Inflammation
Espevik	Terje	Professor	Norway	Inflammation
Fitzgerald	Kate	Professor II	USA	
Flo	Trude Helen	Professor	Norway	Mycobacteria & HIV
Giambelluca	Miriam	Postdoctor	Argentina	System Inflammation
Gidon	Alexandre	Postdoctor	France	Mycobacteria & HIV
Gierman	Lobke	Postdoctor	Netherlands	Pregnancy
Granlund	Atle Van Beelen	Postdoctor	Norway	IBD
Gravastrand	Caroline	PhD candidate	Norway	Inflammation
Grøvdal	Lene Melsæther	Researcher	Norway	Inflammation
Haug	Markus	Researcher	Norway	Mycobacteria & HIV
Husebye	Harald	Researcher	Norway	Inflammation
Håland	Kari	Head of administration	Norway	(from Oct 2018)
Iversen	Ann-Charlotte	Professor	Norway	Pregnancy
Johansson	Ida	Postdoctor	Norway	Autophagy
Kandasamy	Richard Kumaran	Associate Professor	India	System Inflammation
Kannan	Nisha	PhD candidate	India	Mycobacteria & HIV
Kim	Hera	PhD candidate	USA	System Inflammation
Kojen	June Frengen	Staff engineer	Norway	Inflammation
Kovcic	Vlado	PhD candidate	Serbia	Bone disease
Latz	Eicke	Professor II	Germany	
Lian	Tone Aksnes	PhD candidate	Norway	Mycobacteria & HIV
Lien	Egil	Professor II	Norway	
Lindholm	Håvard Takle	PhD candidate	Norway	Regeneration
Louet	Claire	Staff engineer	France	Mycobacteria & HIV
Marstad	Anne	Staff engineer	Norway	Mycobacteria & HIV
Meås	Hany Zakaria	PhD candidate	Egypt	Mycobacteria & HIV
Moen	Ingrid Nyhus	PhD candidate	Norway	Inflammatio

Moharrami	Neda Nejati	PhD candidate	Iran	Inflammation
Mollnes	Tom Eirik	Professor II	Norway	
Mundal	Siv Boon	PhD candidate	Norway	Pregnancy
Nilsen	Kaja Elisabeth	PhD candidate	Norway	Inflammation
Nilsen	Nadra	Researcher	Norway	Inflammation
Niynzima	Nathalie	Postdoctor	Norway	Inflammation
Nonstad	Unni	Staff engineer	Norway	Inflammation
Ostrop	Jenny	Postdoctor	Germany	Regeneration
Oudhoff	Menno	Researcher	Netherlands	Regeneration
Parmar	Naveen	PhD candidate	India	Regeneration
Pettersen	Kristine	Postdoctor	Norway	Autophagy
Richard	Gabriel	Staff engineer	India	System Inflammation
Rokstad	Anne Mari	Researcher	Norway	Inflammation
Ryan	Liv	Staff engineer	Norway	Inflammation
Sandvik	Arne	Professor	Norway	IBD
Serrra	Ignacio Catalan	Postdoctor	Spain	IBD
Sharma	Aditya Kumar	Postdoctor	India	System Inflammation
Silva	Gabriela Brettas	PhD candidate	Brazil	Pregnancy
Skjesol	Astrid	Researcher	Norway	Inflammation
Skovdahl	Helene Kolstad	PhD candidate	Norway	IBD
Spanjers	Roos	Scientific assistent	Netherlands	Regeneration
Sporsheim	Bjørnar	Staff engineer	Norway	
Standal	Therese	Professor	Norway	Bone disease
Starheim	Kristian	Researcher	Norway	Inflammation
Steigedal	Magnus	Researcher	Norway	Mycobacteria & HIV
Steinkjer	Bjørg	Staff engineer	Norway	Inflammation
Stenmark	Harald	Professor II	Norway	
Stenvik	Jørgen	Researcher	Norway	Inflammation
Strand	Trine Aakvik	Staff engineer	Norway	Mycobacteria & HIV
Stødle	Guro	PhD candidate	Norway	Pregnancy
Subbannayya	Yashwanth	Postdoctor	India	System Inflammation
Sundan	Anders	Professor	Norway	Bone disease
Thorsvik	Silje	PhD candidate	Norway	IBD
Ullmann	Sindre	PhD candidate	Norway	Mycobacteria & HIV
Underhill	David	Professor II	USA	
Vik	Randi	Staff engineer	Norway	Inflammation
Westhrin	Marita	Postdoctor	Norway	Bone disease
Wolowczyk	Camilla	PhD candidate	Norway	Autophagy
Yurchenko	Mariia	Postdoctor	Ukraine	Inflammation
Zwiggelaar	Rosalie	PhD candidate	Netherlands	Regeneration
Ørning	Mathias Pontus	PhD candidate	Norway	Inflammation
Østvang	Janne	Head of administration	Norway	(From Jan- Oct 2018)
Åsberg	Signe	PhD candidate	Norway	Mycobacteria & HIV

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Funding and Expenditures 2018

Funding (1000 NOK)	2018
NTNU	26 687
Research Council of Norway (RCN) – Centre of Excellence grant	20 889
Other RCN funding	12 884
Other public funding	14 382
Other private funding	4 162
International funding	1 437
Total funding	**80 441**

Expenditures (1000 NOK)	2018
Personnel and indirect costs	60 718
Equipment	443
Other operating costs	19 280
Total expenditures	**80 441**

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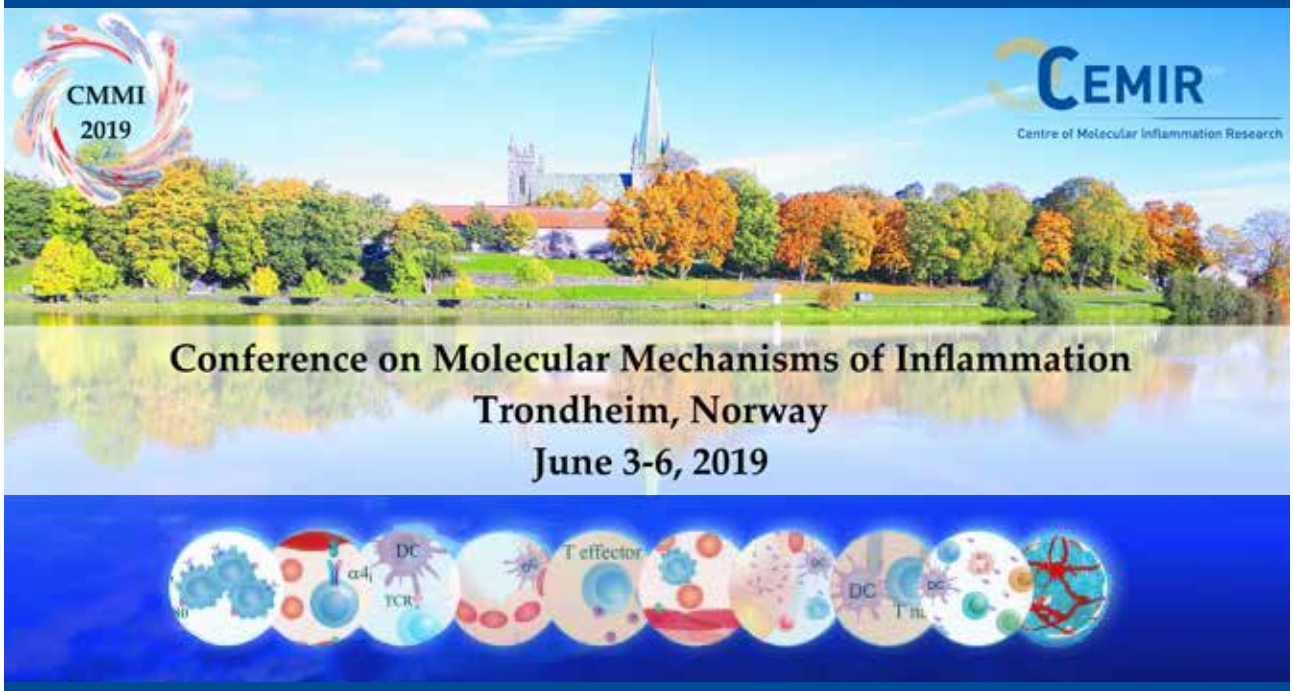

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