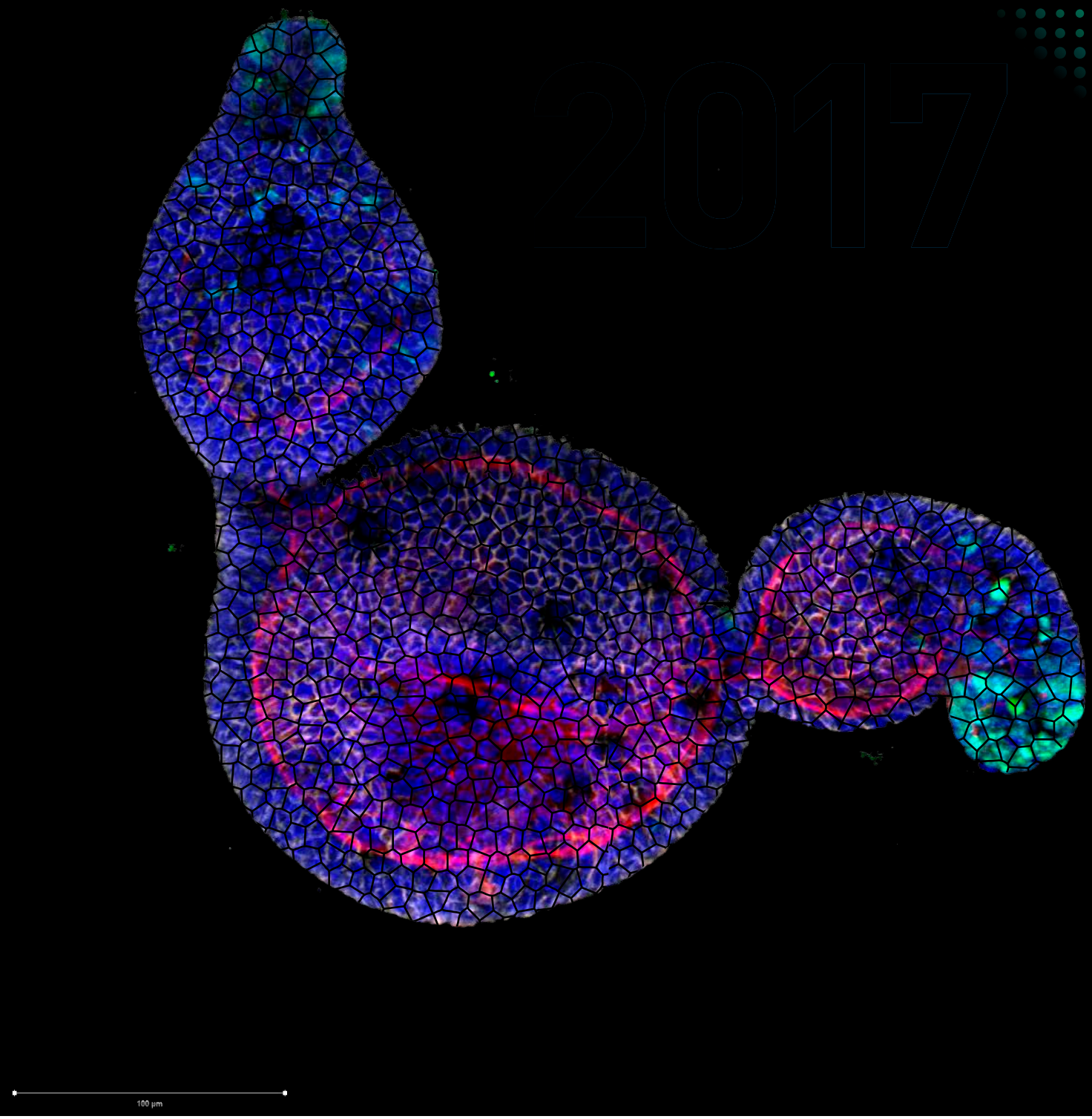
2017



Norwegian Centre of Excellence
The Research Council of Norway

CEMIR
Centre of Molecular Inflammation Research

Table of content

Cover photo made by Mara Martin Alonso:
Maximal projection of a 3D colon organoid growing on matrigel. Colon organoids mimic the organization and cellular population of the intestinal epithelium showing a crypt-like structure enriched in stem cells (Ki67 (green) positive cells). The rest of the intestinal epithelial cells forming a bobble-like structure. In addition to the green cells we se: B-Catenin (grey), Phalloidin (red) and DAPI (blue).

Directors 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 unite scientists across disciplines to get important insight in basic biological and clinical inflammation research. CEMIR is very grateful that the Norwegian Research Council (RCN) recognizes the work CEMIR do to reach its vision.

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 2015, we opened a new BSL3-laboratory, offering the highest level of security for research on viruses and bacteria in Norway.

In October 2017 CEMIR organized a retreat for their employees in Taormina, Sicily, Italy. This place was chosen because of the close scientific collaboration between CEMIR and professor Giuseppe Teti, University of Messina, Sicily, and he was the local organizer for the retreat. This retreat was a great scientific and social success and 60 employees participated in the event.

In 2017 CEMIR was mid- term evaluated by an international evaluation committee appointed by the 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 next 5 years.

CEMIR has grown to be a vibrant and dynamic center with 68 scientific staff members, 16 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 a vibrant 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.

The scientific activities at CEMIR have proceeded with very good progress. CEMIR researchers have published more than 200 articles since 2013, several in high quality journals like Nature, Nature Immunology, Autophagy, PNAS and J Immunol. Nineteen PhD students have completed their theses at the centre since 2013.

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 theme names and milestones to be accomplished for the five last years. 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.

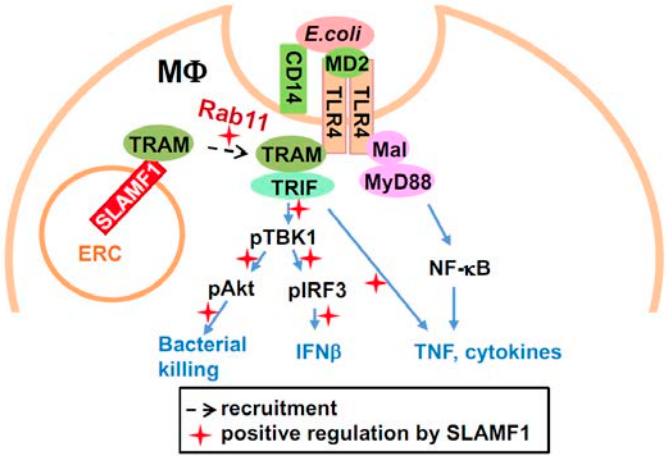
Terje Espevik

Terje Espevik
Centre director

CEMIR RESEARCH THEMES

Signalling pathways and vesicle transport systems that regulate inflammatory responses

Theme Manager: Professor Terje Espevik



CD150 is a positive regulator of TLR4 signalling and controls intracellular killing of bacteria.

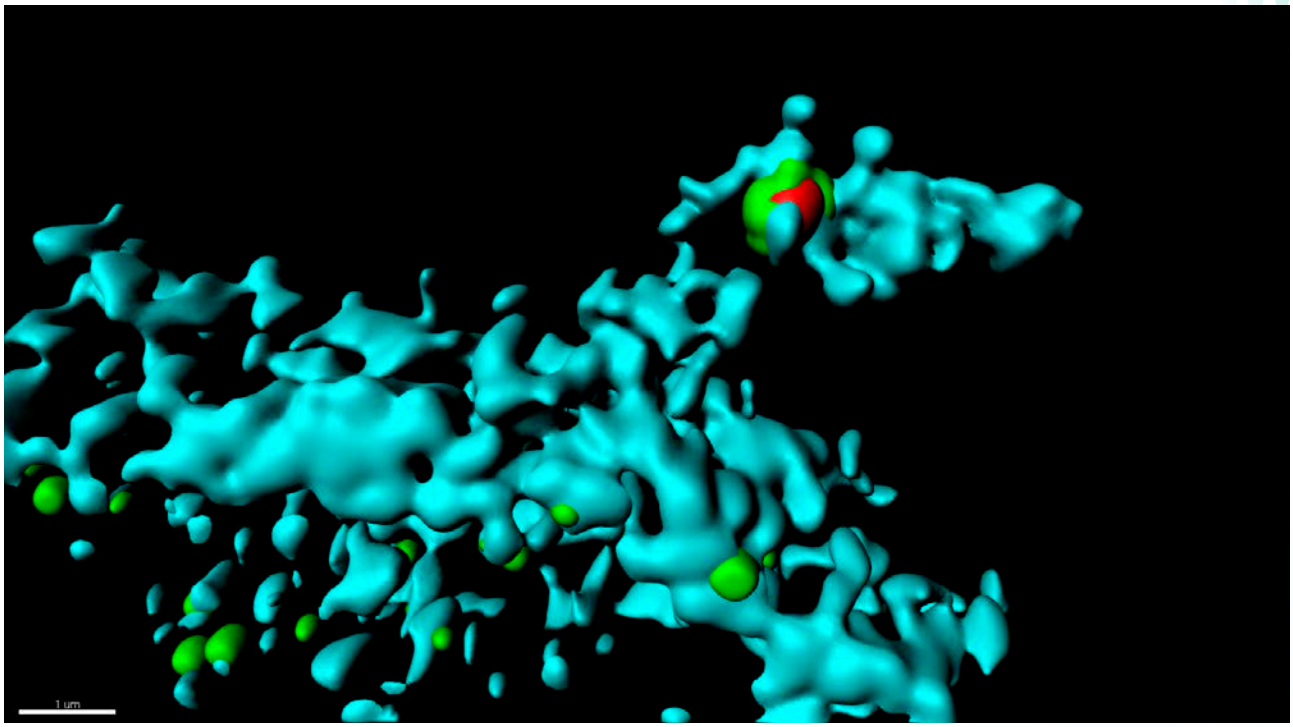
In the presence of systemic infection, microbial pathogens induce strong inflammatory- and coagulation activation, leading to sepsis and septic shock. Also, an anti-inflammatory response is induced during sepsis that can contribute to secondary infections. Severe bacterial infections may lead to high amounts of type I IFNs that can result in production of immunosuppressive molecules increasing the risk for secondary infections. The main aim of this theme is to find new principles of Toll-like receptor (TLR) signalling resulting in type I interferons from endosomes and phagosomes. A second aim is to find ways to inhibit inflammatory responses by targeting TLRs and the complement system.

Main activities 2017

The induction of type I IFNs by various types of bacteria in different immune cells has gained increased attention in recent years. The impact of type I IFNs on bacterial infections is not clear and spans from immune stimulation to immune suppression. However, several reports have suggested that induction type I IFN contributes to the progression of septic shock. Lipopolysaccharide (LPS) from Gram-negative bacteria is recognized by TLR4 and activates two distinct signalling pathways. One of the pathways needs the sorting adapter protein TRAM, and the signalling adapter TRIF for inducing IFN-ß.

We have discovered that CD150, which belongs to the signaling lymphocyte activation molecule family (SLAMF) receptors, strongly interacts with TRAM. CD150 is known to modulate a wide range of functions, such as myeloid cell and lymphocyte development, and T- and B cell responses to microbes and parasites. Moreover, CD150 serves as microbial sensors and can control phagosomal maturation. To our surprise, we have found that CD150 regulates macrophage responses to Gram-negative bacteria through interaction with the Toll-receptor-associated molecule TRAM. We found that CD150 is required for TLR4-mediated induction of IFN-ß and for killing of Gram-negative bacteria by human macrophages. CD150 controls trafficking of TRAM from endocytic recycling compartment (ERC) to *E. coli* phagosomes. In resting macrophages CD150 is localized to ERC, but upon addition of *E. coli* it is trafficked together with TRAM from ERC to *E. coli* phagosomes in a Rab11-dependent manner. These findings point to CD150 as a target for inhibiting harmful overstimulation of the innate immune system that may occur during severe bacterial infections. Manuscript describing these data has been accepted in J. Cell Biol.

TLR8 is the major endosomal sensor of degraded RNA in human monocytes and macrophages. It has been implicated in the sensing of viruses and more recently also bacteria. We previously identified a TLR8-IFN regulatory factor 5 (IRF5) signaling pathway that mediates IFN-ß and interleukin-12 (IL-12) induction by *Staphylococcus aureus* and is antagonized by TLR2. The relative importance of TLR8 for the sensing of various bacterial species is however still unclear. We here compared the role of TLR8 and IRF5 for the sensing of Group *B Streptococcus* (GBS), *S. aureus,* and *E. coli* in human primary monocytes and monocyte-derived macrophages (MDM). We have found that TLR8-IRF5 signaling is more important for the



3-D super resolution microscopy of TRAM at the phagocytic cup of a human macrophage. The image shows the accumulation of the TLR4 adapter TRAM at the E. coli binding site located on a plasma membrane extension (philopodia) positive for F-actin. 3-D data imaging data was obtained at an optical resolution of 70 nm using 3-D super resolution microscopy. TRAM channel (green), E. coli channel (red) and F-actin (cyan). Photo: Astrid Skjesol and Harald Husebye

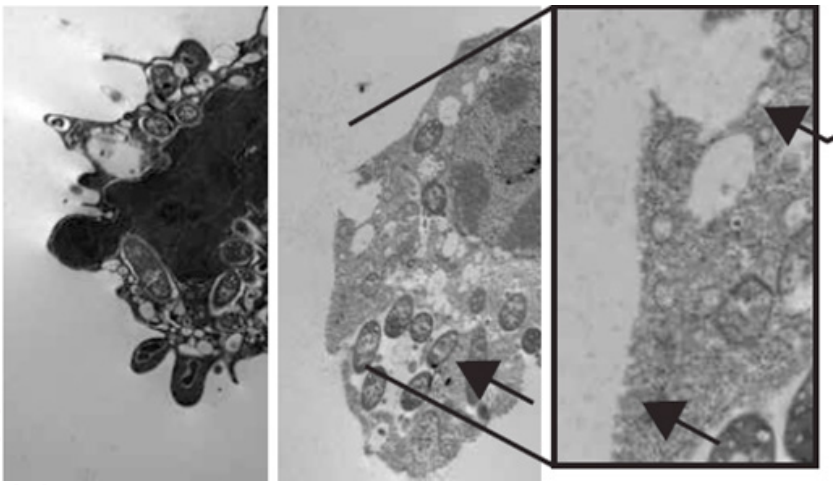
sensing of GBS than for stationary grown *S. aureus*, likely due to reduced resistance of GBS to phagosomal degradation and to a lower production of TLR2 activating lipoproteins. TLR8 does not sense viable *E. coli*, while IRF5 still contributes to *E. coli*-induced cytokine production, possibly via a cytosolic nucleic acid sensing mechanism. This work was published in Front Immunol in 2017. Another focus of this theme has been to inhibit inflammatory responses by targeting TLRs and the complement system. Through a close collaboration with the Mollnes group we have constructed and characterized a chimeric recombinant anti-human CD14 IgG2/4 CD14 with minimal ability to activate complement and bind to FcRs. The original anti CD14 hybridoma (18D11) was generated in the laboratory of Espevik. The Mollnes group has previously found that the combination of 18D11 and complement inhibition is a particular potent attenuator of bacterial inflammatory responses in human whole blood (reviewed in J. Leukoc. Biol. 2017). Recently, the Mollnes group demonstrated that the combined inhibition of complement factor C5 and CD14 efficiently attenuated the inflammatory response also in a porcine model of meningococcal sepsis (J. Intensive Care. 2017).

Major achievements in 2017

- We discovered that the Ig-like receptor molecule CD150 enhances production of type I interferon induced by Gram-negative bacteria through modulation of MyD88 independent TLR4 signaling. This makes CD150 a potential target for controlling inflammatory responses against Gram-negative bacteria.
- We published that Toll-like receptor 8 is a major sensor of Group *B Streptococcus but not Escherichia coli* in human primary monocytes and macrophages. (Stenvik et al. Front Immunol. 2017)
- We published that combined inhibition of C5 and CD14 efficiently attenuates the inflammatory response in a porcine model of meningococcal sepsis. (Mollnes et al., J. Intensive Care. 2017)

The molecular basis for inflammasome activation

Theme Manager: Professor Egil Lien



Cell death with aspects of both apoptotic and pyroptotic death following bacterial infection. Left to right: an apparent apoptotic cell, and an early pyroptotic cell with a close-up of a membrane burst. Photo: Dan Weng

Inflammasomes have been defined as multi-molecular complexes that process pro-caspase-1 into the active enzyme. Recent advances, including work performed under this theme, have suggested that other caspases like caspase-11 and caspase-8 also can participate in inflammasome processes. These caspases mediate inflammasome-induced cell death called pyroptosis. The inflammatory caspases direct maturation of pro-forms of cytokines IL-1ß and IL-18 into active forms. These cytokines play key roles in the host defenses towards a number of infections, but can also be harmful in some inflammatory disorders. The work in this theme is focused on describing mechanisms leading to inflammasome activation, and to study implications of inflammasome-mediated inflammation.

Main activities

During this period we have investigated roles of several components of inflammasome complexes in bacterially induced cell death, working with Salmonella and Yersinia infection systems. These two bacteria both have type III secretion systems that are key to their inflammasome activation, but have different set of secreted effectors (protein toxins) that are injected into the host cells. We have described how several of these bacterial effectors manipulate the host inflammasome system to their advantage. However, host responses are triggered in attempts to counteract this manipulation. A new inflammasome complex member called Gasdermin D (GSDMD) has very recently been suggested as a mediator of pyroptotic cell death as cleaved N-terminal fragments oligomerize to pores in cytoplasmic membranes. We have identified a new RIP kinase/caspase pathway leading to bacterial activation of Gasdermin D.

This activation also leads to flux of cytokines (like IL-1 and IL-18) and water through these pores, increasing inflammation and cell swelling and accelerating pyroptotic death. We are also conducting CRISPR/Cas9 mediated bacteria-induced cell death screens and are characterizing hits from our screens. Finally, we are investigating new methods of delivering vaccines using glucan particles packed with antigens and a mixture of adjuvants (stimulators of Toll-like receptors and inflammasomes) and optimizing delivery and compositions of such vaccines for highest effect against bacterial infection.

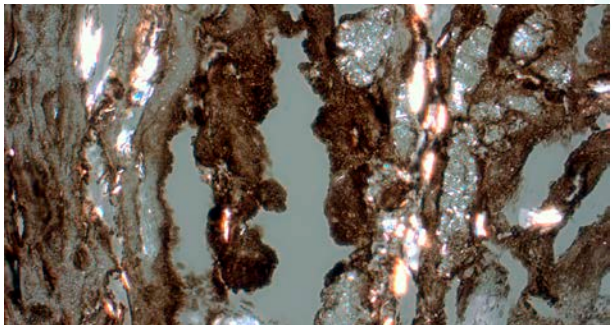
Overall, the activities under this theme have characterized several new players in regulation of inflammation and inflammasomes, both on the host and on the microbial side.

Major achievements in 2017

- Identified novel molecular pathways triggering bacterially-induced cleavage of Gasdermin D
- Described new details on how bacterial effector molecules manipulate inflammasome activation
- Defined new vaccines containing TLR and NLR stimulators that are highly effective in protecting against infections

Inflammatory Responses induced by Cholesterol

Theme Manager: Professor Jan Kristian Damås



Histological section of a human carotis plaque from a patient with large-vessel occlusion following advanced carotid atherosclerosis. Brownish color are complement whereas cholesterol crystals are bright structures. (Inverted fluorescence microscope, 40x objective). Photo: Anne Mari Rokstad

Cholesterol crystals (CC) are known to play an essential role in development of atherosclerosis. Inflammation has become a central focus in atheroma development, and cholesterol itself can cause inflammation in its crystalline form by activating the NLRP3 inflammasome. Our main aim is to uncover the mechanisms by which CC induces inflammatory responses in monocytes and endothelial cells and explore novel treatment strategies in atherosclerosis such as blocking of CC-induced inflammation as well as inhibition of downstream complement activation and cytokines.

Main activities in 2017

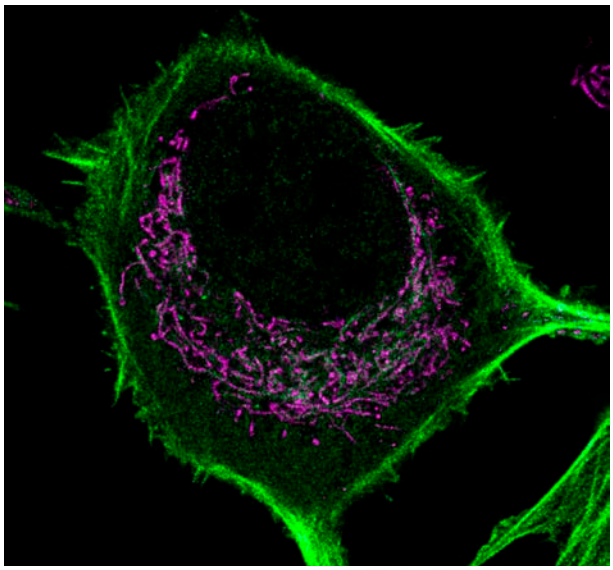
The research focus this year has been on the role of complement activation for CC induced inflammatory responses. We have been exploring how ß-cyclodextrin (BCD) may attenuate CC-induced inflammation. Previously we showed that BCD removes cholesterol from cultured cells, and we have performed several experiments showing that this substance also may alleviate CC-induced inflammation. This year we have explored how BCD reduces CC-induced inflammation through modulating complement activation. We have also examined the regulation of NLRP3-activation by interleukin-27 and how CC induce tissue factor pathway inhibitor (TFPI) and cytokine expression in M2-polarized macrophages. The clinical aspects of inflammation in atherosclerosis have been examined by performing several studies of inflammatory markers in the HUNT study. The diagnostic and prognostic properties of PCSK9, extracellular matrix proteins (e.g. COMP and YKL-40) and markers of T-cell and monocyte activation (e.g. sCD163, sCD14 and sCD25) have been explored in patients with myocardial infarctions (MI) and in healthy controls. We have performed genetic studies in offsprings from preeclamptic pregnancies and controls looking for associations between genetic variants and risk for developing preeclampsia. In collaboration with the Departments of Cardiology at St. Olav's Hospital and Oslo University Hospital (Rikshospitalet and Ullevål Hospital) we have started the inclusion in the "Effect of the interleukin-6 receptor antagonist tocilizumab as an adjunct to primary percutaneous coronary intervention in ST elevation myocardial infarction - a randomized, double-blind, placebo controlled study (the ASSAIL-MI trial).

Major achievements in 2017

- Showed that BCD reduces cholesterol crystal-induced inflammation through modulating complement activation (Bakke SS, et al. J Immunol. 2017;199:2910–2920).
- Discovered that interleukin 27 is increased in carotid atherosclerosis and promotes NLRP3 inflammasome activation (Gregersen I, et al.. PLoS One. 2017;12:e0188387).
- Showed that both isoforms of TFPI are present in advanced atherosclerotic plaques and that anti-inflammatory M2 macrophages may be a potential source of TFPI (Espada S, et al. Biochem Biophys Res Commun. 2017;491:442–448).
- Showed that CC induce TFPI and cytokine expression in M2-polarized macrophages through activation of the ER stress pathway and that TFPI has a protective effect against TNF- and IL-6 mediated inflammation (Stavik B, et al. Thromb Res. 2017;155:31–37).
- Published a review paper summarizing how cholesterol crystals employ the complement- and inflammasome system interact to mount inflammatoryÐesponses. (Niyonzima N, et al. Mol Immunol. 2017;84:43–50).
- Discovered the first genome-wide significant susceptibility locus (rs4769613; P = 5.4 × 10–11) in 4,380 offsprings from preeclamptic pregnancies and 310,238 controls (McGinnis G, et el. Nat Genet. 2017;49:1255–1260).
- Showed that he occurrence of major coronary events was increased among women with preeclampsia (1980–2002) (Riise Hk, et al. J Am Heart Assoc. 2017;6: pii: e004158).
- Demonstrated that The minor (G) allele of the intronic SNP rs17367504 in the gene methylenetetrahydrofolate reductase (MTHFR) was associated with a protective effect on preeclampsia (Thomsen LC, et al. J Hypertens. 2017;35:132–139).
- In the HUNT study, we showed that circulating PCSK9 is not independently associated with risk of MI in healthy individuals (Laugsand LE, et al. JACC Basic Transl Sci. 2017, in press). Further, we demonstrated that high levels of COMP and YKL-40 were associated with lower risk of incident MI(Ueland T, et al. Eur J Prev Cardiol. 2017;24:1161–1167). And we found that markers of T cell and monocyte/macrophage activation were not independently associated with risk of MI in healthy individuals (Ueland T, et al. Int J Cardiol. 2017;243:502–504).
- Demonstrated that the interleukin-6-receptor antagonist tocilizumab affects soluble endothelial markers and coronary endothelial function in non-ST-elevation myocardial infarction (Holte E, et al. Heart. 2017;103:1521–1527).

Infection, Inflammation & Autophagy

Theme Manager: Professor Trude Helen Flo



Super-resolution STED microscopy image of NIH-3T3 fibroblast with actin (LifeAct-mNeonGreen) and mitochondria (TMRE, red). Photo: Kai Sandvold Beckwith.

Cells frequently experience stress resulting in activation of PRR responses and induction of autophagy. A process that is essential for cellular homeostasis and, if defective, leads to disorders like degenerative diseases, cancers, infections, inflammation and cardiovascular disease. We aim to define novel relations between oxidative stress, signalling through PRRs and autophagy in inflammatory diseases, including mycobacterial and HIV infections where the focus is molecular host defence mechanisms involved in immunity to mycobacteria and HIV, and virulence strategies employed by these pathogens to parasitize host cells.

Main activities 2017

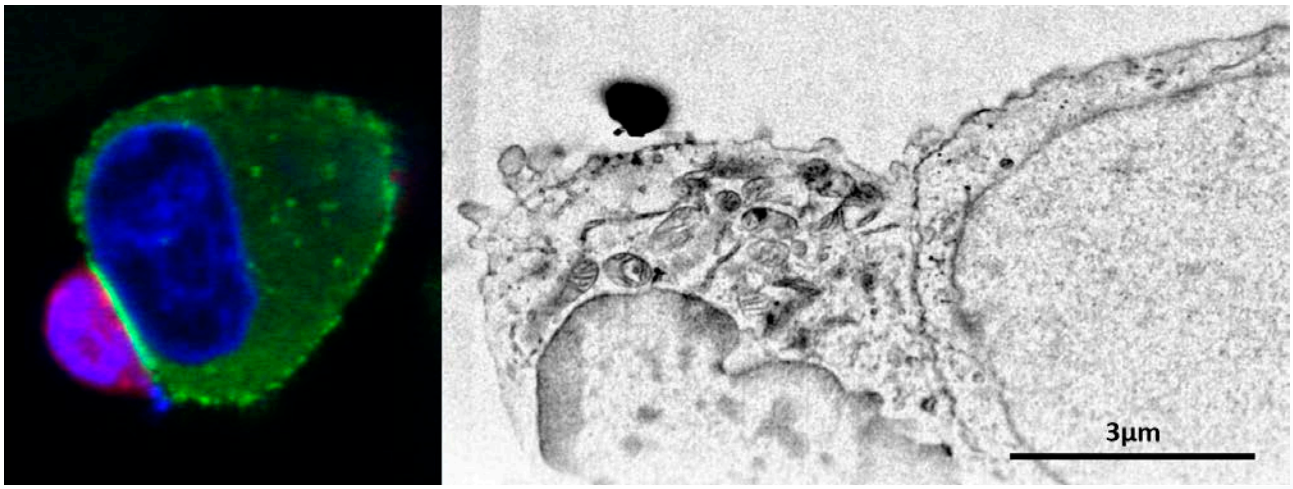
One of the highlights of this theme was completion of a study connecting the spatiotemporal dynamics of trafficking and inflammatory signalling by *Mycobacterium avium* in human primary macrophages. The work was published in PLOS Pathogens (PMID: 28806745) and shows that *M. avium* hides in a compartment from where no inflammatory signalling is generated, whereas *M. avium* degraded in phagolysosomes engages TLR7/8. Targeting the mycobacterial compartment, preventing its formation or forcing mycobacteria out of it should be of therapeutic value as host-directed therapy to face the challenge with antimicrobial resistance. To better characterize it we aim to isolate and sort *M. avium* and *M. tuberculosis* compartments for proteomic analyses.

Different from *M. avium*, *M. tuberculosis* can escape from phagosomes. By live single-cell imaging and high-resolution 3D electron microscopy we find that this leads to NLRP3 inflammasome activation followed by IL-1ß secretion and cell death by pyroptosis. Mycobacteria express several type VII secretion systems, and in 2017 we established that loss of the ESX-3 secretion system in leads to decreased survival of *M. smegmatis* in macrophages. We also established that the reduction in survival leads to an increase in presentation of antigens to T-cells, a discovery with potential impact on vaccine development. In addition, together with research collaborators, we have discovered compounds that we currently investigate for the ability to inhibit ESX-3 function.

This year we have also discovered that T-cells respond to activation of TLR8 by endosomal HIV with cytokine secretion, and will complete this work in 2018. In collaboration with the systems inflammation group we have completed a CRISPR/Cas9 knockout screen on HIV-infected T-cells for discovery of genes restricting or facilitating viral growth. We are now in the progress of validating the screen and following up on some of the targets.

Autophagy is a core process to maintain cellular homeostasis during starvation, oxidative and protein folding stress. In a growing tumor, cancer cells will face reduced availability of nutrients and oxygen. We published this year that several cancer cells secrete compounds that induce autophagy (PMID: 28515477). One such compound is IL-6 that combines with soluble IL-6 receptor and induces autophagy muscle cells and reporter cells by IL-6 trans-signaling. IL-6 is one of the candidates for causing the severe wasting syndrome cancer cachexia. In line, we find autophagy-inducing activity in serum from cancer patients associated with weight loss.

We have previously found that n-3 PUFAs induce autophagy in epithelial cells in a lipid selective manner and promotes cell survival in response to stress (PMID: 26237736, 26585906). Importantly, the same mechanism may also explain the anti-inflammatory activities of n-3 PUFAs; we found that elevated autophagy and oxidative stress activated by n-3 PUFAs in macrophages dampen a selective set of pro-inflammatory cytokines (PMID: 28820283). Some cancer cells have a particular challenge with protein folding. Myeloma cells are transformed plasma cells producing high amounts of immunoglobulins and myelomatosis is now treated with proteasome inhibitors. We have recently published that different proteasomal inhibitors may have different modes of action



Correlative light and electron microscopy of a virological synapse formed between a HIV-infected HeLa cell and a T cell. Left: confocal image with HIV-protein in green, T cell in red and nuclei in blue. Right: Scanning electron microscopy image of the same two cells. Photo: Marianne Sandvold Beckwith.

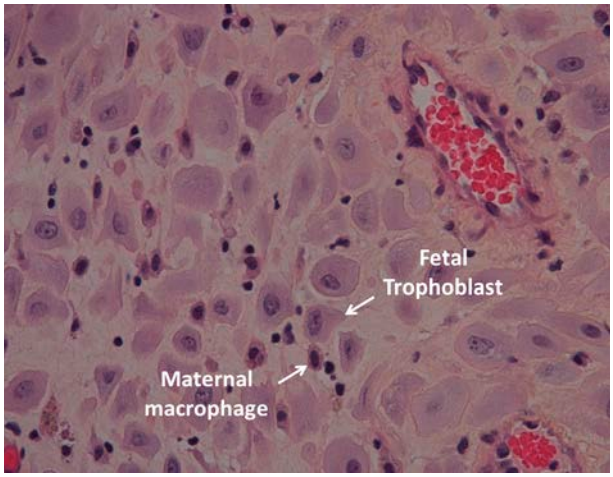
in myeloma cells (PMID: 27683126, 27421095). We now find that myeloma cells actively release protein aggregates containing immunoglobulins and SQSTM1/p62 and hypothesize that this is a novel cell survival mechanism.

Major achievements in 2017

- Established that persistent mycobacteria evade an antibacterial program mediated by phagolysosomal TLR7/8/MyD88 in human primary macrophages (Gidon et al., PLOS pathogens PMID:28806745)
- Established at the single-cell level and in a temporal manner that *M. tuberculosis* activates NLRP3 inflammasomes followed by IL-1ß release and cell death by pyroptosis
- Discovered that T-cells respond to synthetic RNA and endosomal HIV with innate cytokine production, possibly mediated by TLR8
- Established that TLR8 ligands re-activate HIV from latency in HIV patient cells
- Finished a CRISPR screen to identify HIV restrictive and permissive factors in T-cells
- Identified putative *M. avium* virulence genes from mice infected with a *M. avium* transposon mutant library
- Established a role for the ESX-3 secretion system in survival of *M. smegmatis* in macrophages
- Identified a novel small molecule inhibitor of mycobacterial type VII secretion systems
- Established that cancer cells secrete compounds including IL-6 that induce autophagy locally and systemically in cancer cachexia
- Established that n-3 poly-unsaturated fatty acids induce inflammatory tolerance by formation of KEAP1-containing SQSTM1/p62-bodies and activation of NFE2L2 (Mildenberger et al,. Autophagy PMID:28828283)
- Discovered that myeloma cells actively release Ig- and SQSTM1-containing aggregates

Inflammation underlying preeclampsia and atherosclerosis

Theme manager: Professor Ann-Charlotte Iversen



Representative picture of maternal-fetal interaction in third trimester decidua stained with hematoxylin-erythrosine-saffron (HES) at CMIC, NTNU. Decidual tissue was obtained by vacuum-suction of the uterine wall, after C-section. Photo: Gabriela Silva.

Inflammation plays a key role in cardiovascular disease, a major cause of illness and death worldwide, with gender-specific manifestations. Pregnancy is a natural state of low-grade inflammation and a stress test to the cardiovascular system. Women with preeclampsia have doubled risk for cardiovascular disease and develop atherosclerosis-like lesions in uterine wall arteries during pregnancy. This suggest shared underlying mechanisms for these vascular diseases. Inflammatory mediators like oxidized lipoproteins and cholesterol crystals are implicated, but with largely unknown molecular action. We hypothesize that inflammatory danger response by pattern recognition receptors (PRRs) is central to preeclampsia pathogenesis and the gender specificity of cardiovascular disease. In this theme, we aim to determine PRR-initiated inflammation underlying preeclampsia and cardiovascular disease.

Main activities in 2017

Extensive quantitative immunohistochemistry analysis comparing placental inflammatory mechanisms are revealing importance for placental inflammation in the pathogenesis of preeclampsia and fetal growth restriction. Inflammatory activation is strongly associated to the fetal cell layer covering the placenta and directly interacting with maternal blood, highlighting a central role for PRR-mediated inflammation at the main maternal fetal interaction site. In uterine wall arteries, maternal-fetal cellular communication and atherotic lesions with foam cells are defined. Inflammasome NLRP3 and cholesterol accumulation are assessed in both the maternal and fetal portion of the placenta. PRR mechanisms identified in patient samples are functionally assessed by PRR-activation studies in cultured placental explants. The lack of objective immunohistochemistry quantification methods has led to establishment of a novel automated image based quantification method allowing for assessing protein expression levels at distinct cellular densities, providing a valuable tool for tissue expression studies. Metabolomic profiling is being further developed for causal classification of the placental disease component of preeclampsia and fetal growth restriction. This classification will be important for the targeted study of inflammatory mechanisms we are undertaking. Novel maternal and fetal 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.

Major achievements in 2017

- Discovered a potent PRR-mediated inflammatory role for the fetal trophoblasts covering placental structures and interacting with maternal blood in preeclampsia (Stødle, PhD thesis, 2017).
- Revealed a pleiotropic protective gene associated with both preeclampsia and non-gestational hypertension in the HUNT Study (Thomsen et al, J Hypertension, 2017)
- Identified the first preeclampsia risk gene in the fetal genome in the EU project InterPregGen (McGinnis et al, Nature Genetics, 2017)
- Revealed how the increased risk of cardiovascular disease following preeclampsia is affected by parity, preterm delivery and fetal growth in the Cohort of Norway (CONOR) (Riise, J American Heart Association, 2017).

Inflammatory Bowel Disease

Theme Manager: Professor Arne Sandvik

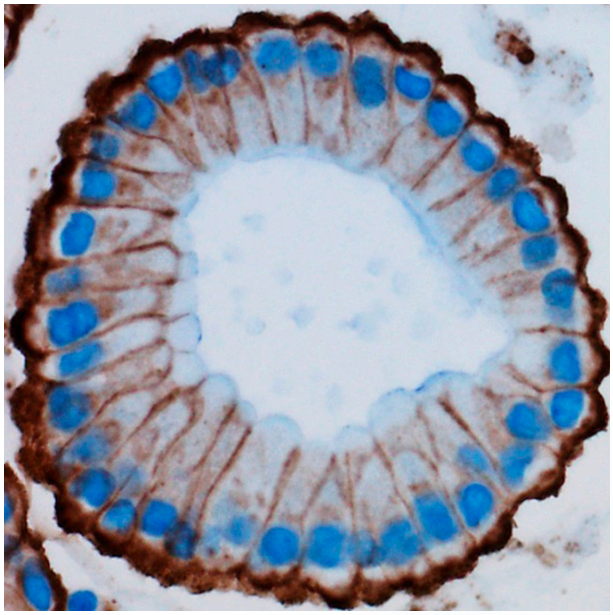
Inflammatory bowel disease (IBD) is a major clinical problem, with up to 3 mill Europeans chronically affected by either ulcerative colitis or Crohn's disease, at an annual cost of approximately € 5,6 bill. Current hypotheses on etiology and pathogenesis include dysfunctional inflammatory pathways including PRRs and autophagy, with presently 204 susceptibility gene loci identified. Hence, we hypothesize that IBD results from an inappropriate inflammatory response to intestinal microbes and endogenous molecules in genetically susceptible hosts. The main aim of this theme is to understand central mechanisms for mucosal homeostasis, how this is disrupted in active disease and subsequently restored in remission.

Main activities in 2017

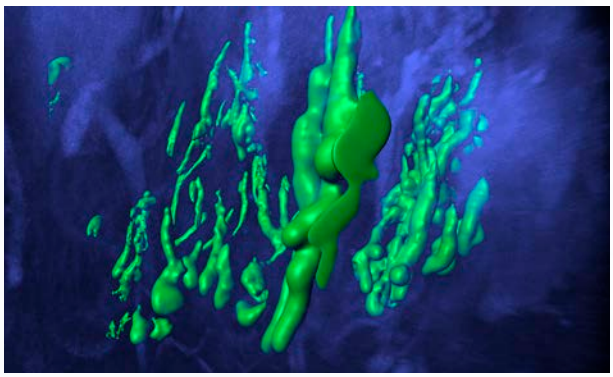
The research group has further strengthened its focus of studying disease mechanisms in patient material, and expanded and refined its IBD biobank. A significant undertaking has been to integrate the SNP analysis in the HUNT biobank and corresponding local IBD data with a large RNASeq dataset, which was generated towards the end of 2017, in eQTL analysis. Another major advance has been to create a large set of colonoids from IBD patients and healthy individuals representing disease heterogenity, these have been used in specific studies on ISG15, CCL20/CCR6, NGAL and other inflammation-relevant molecules involved in IBD. This model is an important element in our collaboration with outstanding research groups abroad. Both here and internationally establishment of small intestinal organoids has proven more difficult than from colon, efforts are ongoing since these will be important particularly in research on Crohn's disease mechanisms.

Major achievements in 2017

- Colonic organoids have been established from a number of patients with ulcerative colitis and Crohn's disease, and healthy controls, and this model is firmly established with mechanistic, IBD relevant studies ongoing.
- SNP genotyping of the IBD biobank is finished, with studies ongoing to utilize these data together with the HUNT SNP dataset in eQTL analysis together with an extensive RNASeq analysis recently done on the same material.
- A position as postdoc shared between the IBD group and Immunobiology/Yale has been advertised, and candidate selection is ongoing. This collaboration has been further strengthened through a visit to Yale by one of the group's researchers.
- The IBD group has developed its translational axis by winning a grant to employ a research nurse at the Gastroenterology Outpatients Unit, and employing an experienced gastrointestinal pathologist as a PhD student within the group.



Colonoid from a patient with ulcerative colitis. Photo: Ingunn Bakke



Immunofluorecence staining of NGAL-positive pyloric metaplasia in chronically inflamed human small intestinal tissue. Prior to staining, the tissue was cleared using the iDisco protocol. The image is a 3D visualization of a Z-stack consisting of 452 images, acquired on a Leica SP8 confocal microscope. Photo: Atle van Beelen Granlund and Silje Thorsvik

Bone destruction caused by cancer and inflammation

Theme Manager: Professor Therese Standal

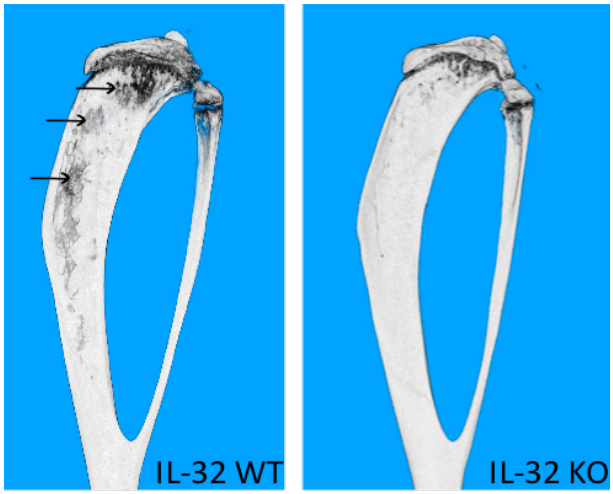
Multiple myeloma is caused by expansion of malignant plasma cells in the bone marrow. Most patients develop an osteolytic bone disease, characterized by increased osteoclastogenesis. The bone disease causes pain, fractures and severely reduced quality of life for the patients. Destruction of bone is also common in cancers metastasizing to bone, for example breast cancer, and in inflammatory diseases such as rheumatoid arthritis (RA). The main aim of this theme is to reveal underlying mechanisms for bone loss associated with cancer and inflammation.

Main activities 2017

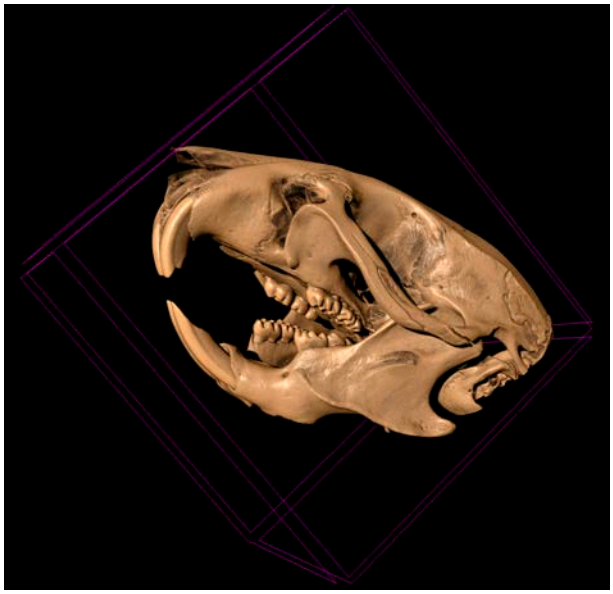
The myeloma bone marrow is hypoxic, and hypoxia may contribute to multiple myeloma disease progression. We found that interleukin-32 (IL-32) increases in response to hypoxia, and that a subpopulation of multiple myeloma patients expresses high levels of this pro-inflammatory cytokine in their cancer cells. We demonstrated that IL-32 is secreted on extracellular vesicles (EV) that have potent pro-osteoclastogenic effects, and that myeloma cells lacking IL-32 lose their osteoclast-promoting properties. Thus, our main activity in 2017 was on the role of IL-32 in myeloma disease progression. We also identified a potential role of immunoglobulins in multiple myeloma bone disease. In this respect, we initiated a collaboration with Prof. Manfred Wuhrer at the Leiden University Medical Center to characterize if glycosylation of immunoglobulins changes during disease progression. In 2017 we also completed a study investigating BMP4 as a therapy for multiple myeloma. For this, we utilized the mouse-human myeloma scaffold model, and examined how adeno-associated virus vector-8 expressing BMP4 (AAV8-BMP4) influenced tumor growth and bone. Interestingly, BMP4 gene therapy reduced tumor growth, but had detrimental effect on bone.

Major achievements 2017

- Demonstrated that IL-32 is secreted from multiple myeloma cells in extracellular vesicles, and that IL-32 in such vesicles promote osteoclast differentiation in vitro and in vivo (Zahoor et al, Blood Advances)
- Generated several IL-32 knock out cell lines using Crispr/CAS9, which will be useful to further explore the role of IL-32 in multiple myeloma disease progression
- Completed a study demonstrating that BMP4 gene therapy in mice inhibits myeloma tumor growth, but has a negative impact on bone (Westhrin/Holien et al, manuscript in preparation)



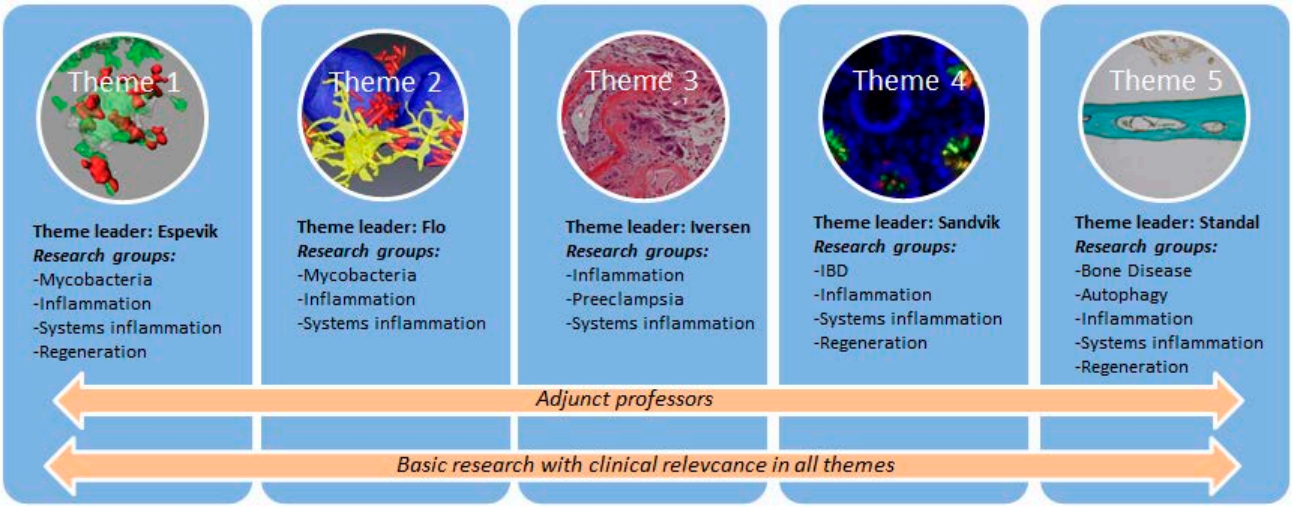
IL-32 is needed for the osteolytic capacity of multiple myeloma cells. uCT image of tibias of mice injected with either WT or IL-32 KO cells. Arrows indicate osteolytic lesions. Photo: Zahoor et al 2017.



Micro-CT scan of mouse skull. The image shows a visualization of a mouse skull, obtained using the SkyScan 1176 in vivo micro-CT scanner. The skull was scanned using 9 µm pixel size resolution,and 360° scan mode. Image re-construction was done using the NRecon software, and 3D visualization was done using the CTvox software. Photo: Glenn Buene

New CEMIR Research Themes and ambitions for 2018

The original themes of CEMIR have been re-organized into 5 new themes to incorporate the research developments, accommodate the recently recruited research groups, and facilitate close interactions between similar research activities across research groups.



Theme 1: 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 MyD88-MAL- and TRAM-TRIF-dependent pathways. 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 CD150 which modulates macrophage responses to microbes in mice. 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.

Ambitions for 2018

- Establish the roles for the Rab11 interacting protein FIP2 and TLR4 adaptor proteins in uptake of bacteria and phagosomal signalling.
- Construct peptides that interfere with CD150 interaction with the Toll-like receptor associated adapter molecule TRAM and test for anti-inflammatory effects.
- Define the molecular mechanisms of how CD150-FIP2-TRAM interactions control inflammatory responses against bacteria and virus.
- Unravel the proteomes of mycobacterial phagosomes supporting or preventing growth
- Further develop correlative florescence light- and 3D electron microscopy for imaging HIV- and mycobacterium infected cells.

Theme 2: Molecular mechanisms of infection and inflammation

Despite extensive global efforts, infectious diseases still cause significant morbidity and mortality. 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 should reveal new therapeutic targets and aid in development of host-directed therapies to be used as adjuncts to antimicrobial treatment of infections.

Ambitions for 2018

- Elucidate mechanisms and dynamics of M. tuberculosis killing of host macrophages
- Elucidating the role of post-translational modifications in cell death pathways
- Determine new regulatory mechanisms for bacteria-induced activation of Gasdermin family members and how secretion systems in Yersinia and Salmonella manipulate inflammasomes
- Use CRISPR screens to identify additional host signalling molecules involved in bacteria-induced pyroptotic and apoptotic cell death, and triggering of inflammasomes
- Targeted CRISPR/Cas9 screens for identification of host factors of HIV and Influenza A virus
- Establish innate T-cell responses to endosomal TLR ligands and HIV

- Elucidate how mycobacteria change over the course of an *Mycobacterium avium* infection
- Establish if putative inhibitors of type VII secretion systems also inhibit the ESX-3 system
- Establishment and use of in vivo bacterial (Citrobacter rodentium) and helminth (Trichuris muris or Heligmosomoides polygyrus bakeri) infection models
- Establish how the FcRgamma chain controls C-type lectin receptors in human phagocytes
- Decoding the commonality and specificity of phosphorylation-based signalling and metabolic rewiring in Toll-like receptor activation
- Examine the association between genetic variations in TLR8 and IRF5 and the susceptibility to bloodstream infection and sepsis in a GWAS study

Theme 3: Molecular mechanisms of inflammation in cardiovascular disease

Inflammation plays a key role in cardiovascular disease and processes like cholesterol crystal (CC) mediated inflammasome activation are central to the pathogenesis. In this new theme 3, we aim to reveal the molecular mechanisms underlying CC induced inflammation and explore ways to inhibit the impact on human disease. 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.

Ambitions for 2018

- Identify PRR mechanisms and cholesterol accumulation at the maternal fetal interface, and define the maternal gestational inflammatory cytokine profile, to understand the maternal and fetal contribution to development of preeclampsia
- Establish novel causal classification of the placental dysfunction in preeclampsia and fetal growth restriction by metabolomic and transcriptomic profiling
- Explore the role of complement and the efficiency of complement inhibition and anti-CD14 treatment in cholesterol induced atherothrombosis
- Characterize molecular mechanisms by which CD5L remodels the inflammatory and metabolic states of macrophages, induce lipid mediators that modulate NF-kB activity, and control ROR nuclear receptors activity
- Study molecular mechanisms for cyclodextrin effects on CC-induced inflammation to support the use of cyclodextrin as a CC targeting drug against atherosclerosis
- Explore the effect of low-calorie diets, weight reduction and microbiota treatment on systemic inflammation
- Complete the study on the effect of the interleukin-6 receptor antagonist tocilizumab in ST elevation myocardial infarction study (ASSAIL-MI study)
- Analyze serum PCSK9 in patients with hypercholesterolemia following non-ST-elevation MI
- To examine the cytokine network during therapy with interleukin-6 receptor antagonism in non-ST-elevation MI
- Expanded collection of patient based biobanks for translational inflammation studies

Identify shared risk genes and risk traits for subgroups of preeclampsia and cardiovascular events and mortality in HUNT and CONOR

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

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. Theme 4 studies the IBD inflammatory process and its consequences at a mechanistic level with hypotheses generated from clinical material.

Ambitions for 2018

- Utilize colonic organoids, and establish permanent cultures of small intestinal epithelial organoids from healthy and IBD mucosa to test hypotheses generated from transcriptome and initial protein network analyses.
- Develop the collaborative Yale/NTNU project, by integrating human NTNU models with ongoing focused microbiome studies in mouse models at Yale.
- Penetrate further, on a detailed mechanistic level, the most promising leads on the inflammatory process in IBD such as the roles of e.g. ISG15, NGAL and CCL20/CCR6.
- Finish collaborative work on Setd7 and the Wnt pathway, and the studies on Lsd1 and Mmp17 in intestinal inflammation and regeneration

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

Cancer cells modulate the tumor microenvironment by secreting factors that promote chronic inflammation, inhibit immune surveillance and disrupt bone homeostasis. Autophagy may support tumor progression by intrinsic cell mechanisms, and by cross talks between tumor cells and stroma. The aim of theme 5 is to understand interactions between tumor cells and the microenvironment at a molecular level.

Ambitions for 2018:

- To continue our studies on the role of IL-32 in multiple myeloma disease progression and mechanisms for IL-32 induction and secretion
- Determine the role of immunoglobulins for bone loss in multiple myeloma
- Describe the mechanism and clinical potential of IAP-antagonists on pathological bone degradation
- Determine how proinflammatory macrophage subtypes differs in their wiring towards different cell-death outcomes: antiinflammatory apoptosis, proinflammatory necroptosis and inflammasome activation
- Finish our studies of the role of the oxidative stress response system in aggressive breast cancer development
- Disrupt hyper-activated genes in metastatic breast cancer cells encoding secreted immune regulators (including CSF1). Analyze the effect on tumor heterogeneity, tumor growth and metastasis
- Characterize novel CSF1R chemical inhibitors generated at NTNU on primary macrophages in culture and evaluate in vivo effects
- Determine how IL-6 trans-signaling induce autophagy in muscle cells in vitro and in vivo
- Find how intracellular protein aggregates is released from myeloma cells and investigate the possible pathophysiological role and if other cell types can do the same

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 3X STED super-resolution laser confocal microscope with a PicoQuant single molecule detection upgrade, and a TIRF microscope. Both these instruments are installed in the new 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 clinical 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 14 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, P. Aukrust and A. Yndestad, 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).

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 and nutrient metabolism are central for survival and attractive targets for drug development, and are currently investigated in our lab both 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 two more senior research scientists, two post docs, four PhD students, two 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 autophagy group (G Bjørkøy), 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, P Aukrust & M Trøseid (OUS, TB & HIV), E Rubin (Harvard, mycobacteria), N Reiling (Research Center Borstel, mycobacteria), K Prasad (Inst Bioinformatics Bangalore, proteomics), M Lerm (Linkøping University, TB screens).

The Autophagy and Oxidative Stress Defense Group

The autophagy group focuses on how this intracellular degradation route is controlled by external factors in inflammation and cancer. We have established that both autophagy and our oxidative stress defense system is induced by n-3 polyunsaturated fatty acids (PUFAs) in both normal epithelial cells and macrophages. For the macrophages, this response results in a dampened reaction to inflammatory stimuli. These responses contribute to our understanding of how disease preventive mechanisms can be mobilized at a cellular level. Now, we study how cancer cells derived compounds suppress macrophages and novel chemical compounds affecting macrophage activity. To identify signaling substances that control macrophages we use a breast cancer metastasis model in immunocompetent mice (4T1) and combine proteomic approaches and RNA sequencing on the model and in silico data mining of patient data to generate hypotheses that is tested by gene editing of cancer cells. For chemical compound screens, we test novel compounds designed and synthesized by our collaborators at NTNU and use novel imaging approaches to monitor effects in macrophages in culture, tumors and tissues.

Degradation of cellular proteins by autophagy mobilize amino acids during starvation. The degradation of cellular proteins is strictly controlled but poorly understood. Cancer cachexia is a severe complication that affect many cancer patients. The condition is induced by the tumor and is characterized by dramatic loss in body weight and muscle proteins. We have found that blood samples 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 collaborate closely with other groups at CEMIR and NTNU for macrophage and cancer biology, imaging and synthetic chemistry. We collaborate with the groups of 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 Professor David Hume and Dr. Clair Pridans at the University of Edinburgh and the Max Planck Lead Drug discovery Center in Dortmund with manager Dr. Bert Klebel.

The Research Group of Inflammation and Genetics in Pregnancy

Pregnancy is a stress test to the cardiovascular system and the hypertensive disorder preeclampsia is considered cardiovascular disease in pregnancy. Two main causative components include placental dysfunction characterized by harmful inflammation in specialized fetal cells (trophoblasts), 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 developing in uterine wall arteries and identification of systemic disease related cytokine profiles. The current lack of diagnostic placental dysfunction markers underlies our molecular profiling and risk gene analysis by omics-technologies to characterize and identify biomarkers of different variants 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, Kjell 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 in the world's largest pregnancy based cohort collaboration for genetic studies. We work closely with other researchers at CEMIR and the core facility CMIC, particularly linked to the molecular studies of lipids and cholesterol crystals and activation of inflammasomes, TLR2 and TLR4 (Inflammation group).

The Research Group is led by Professor Ann-Charlotte Iversen. In 2017, the group counted 9 persons; Professor Iversen, 1 post doc, 3 PhD students, 3 MD PhD students, one MD student and one Master student. PhD student Guro Stødle and Master student Zahra Pervaiz defended their theses and two new students joined the group in 2017.

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-diciplinary, 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), 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. Hypoxic and ER stress and a low grade, chronic inflammation characterizes the myeloma bone marrow. Our research is centered on identifying inflammatory factors present in the bone marrow microenvironment that influence differentiation or activation of bone cells. The underlying hypothesis is that the causes of bone loss associated with inflammatory diseases and cancer might be common.

Our group profits from a close collaboration with clinicians and researchers at the multiple myeloma group headed by Anders Sundan at NTNU. In close collaboration with the Hematology Department at St. Olavs Hospital and the Regional Biobank we have access to well characterized samples from myeloma patients.

We also benefit from collaboration with the Nordic Myeloma Study Group, in particular with Niels Abildgaard at Odense University Hospital in Denmark. In collaboration with Anton Martens at the VU University Medical Center, Amsterdam, we have established a mouse model for multiple myeloma here in Trondheim. This model allows for a reconstruction of a human hematopoietic environment in scaffolds that are subsequently implanted in immune compromised mice. This model has given us new opportunities in terms of in vivo experiments. 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 strengthen 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.

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, aberrant repair can be the initiation of tumorigenesis. We are interested in the cellular and molecular mechanisms that trigger and execute these reparative and regenerative processes, and use the intestine as our working model. Commonly, there is interplay between various cell types, each giving and receiving cues that together orchestrate an optimal response. In addition, there are biomechanical cues such as tissue stiffness that can modulate these responses. Our group combines (bio)-chemical and cell biological tools with in vivo models and in vitro organoid model systems to study these processes.

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 in various biological processes, a collaborative effort will be published in early 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 contributed to recent work from Dr. Alicia Garcia Arroyo (CNIC, Madrid) on metalloproteinases and we will continue this fruitful collaboration in the future. 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 provides support to analyze RNA and ChIP sequencing using bioinformatics.

This group started in 2016, is led by Menno Oudhoff, and additionally consists of 2 Postdocs, 1 PhD student, and 1 Research Assistant. In 2018, our group will grow with 1 Postdoc, 1 PhD student, and 2 MSc students.

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 and post-translational modifications (PTMs) in addition to metabolic reprogramming. The systems inflammation research group aims to specifically study the role of two major PTMs – phosphorylation and ubiquitinome; and metabolic reprogramming; in antiviral signaling and inflammation using state-of-the-art systems-level approaches using 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, 2 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) Geir Slupphaug (NTNU Proteomics Core). Our international collaborators include Giulio Superti-Furga (Center for Molecular Medicine, Vienna, Austria), Rune Linding (University of Copenhagen, Copenhagen, Denmark), Keshava Prasad (YU-IOB 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).

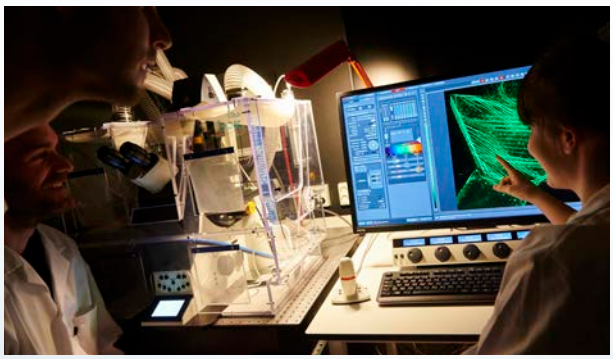
LABORATORY FACILITIES

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

CEMIR hosts first-class laboratories with state-of-the-art equipment for performing research on cells, tissues and microorganisms:

- high resolution STED confocal microscope
- total internal reflection fluorescence (TIRF) microscope
- live cell- and spinning disk confocal microscopes
- image flow cytometer
- cell sorter
- a confocal microscope installed in a biosafety level 3 facility

Technicians are taking care of the important cell-sorting task at CEMIR.



Leica SP8 STED is used in the research at CEMIR.

USE OF THE IMAGING CORE FACILITY

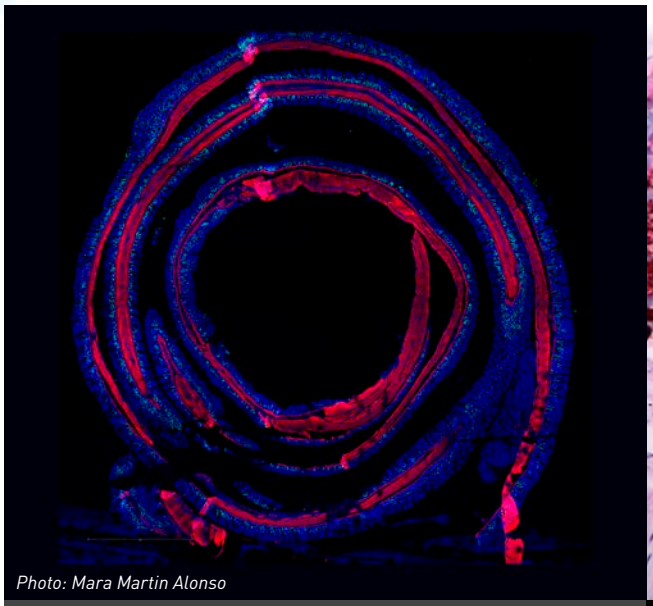


Photo: Mara Martin Alonso

Photo: Atle van Beelen Granlund

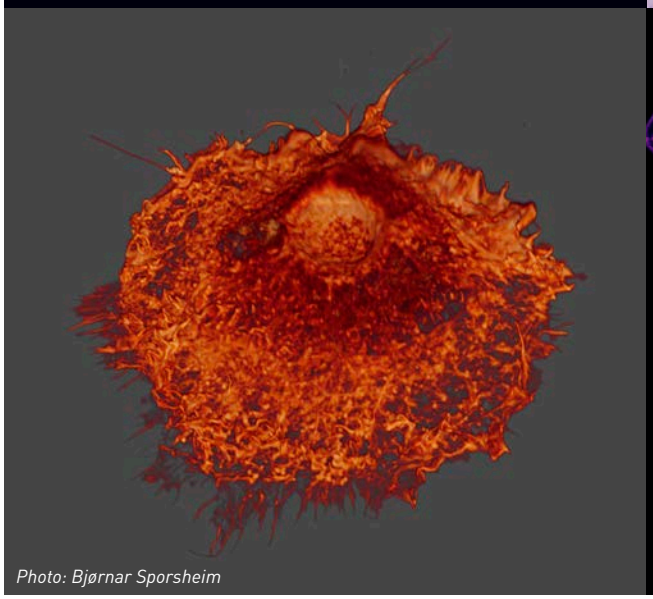


Photo: Bjørnar Sporsheim

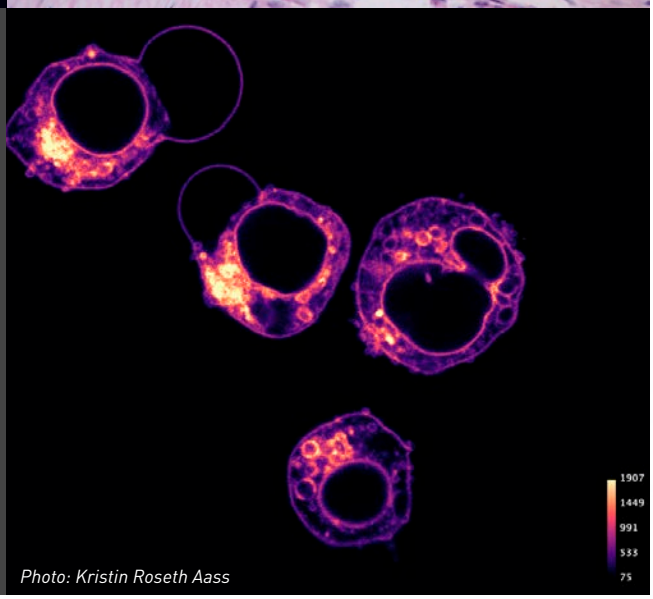


Photo: Kristin Roseth Aass

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, http://www.ntnu.edu/mh/cmic. The CEMIR director is the scientific leader for this core facility. CMIC is closely integrated with the CEMIR's laboratories and its research groups, and CEMIR scientists are the biggest user group of CMIC. The core facility offers several services: standard confocal microscopy and live cell imaging, fully automated high-throughput image acquisition, image visualization and image processing, immune histochemistry and electron microscopy.

In 2014, a super resolution light microscope and a total internal reflection fluorescence microscope were installed at CMIC and placed in the CEMIR laboratories. In 2016, CMIC purchased a PicoQuant single molecule detection (SMD) upgrade for our Leica SP8 STED 3X super-resolution microscope. This add-on is in particular 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.

COOPERATION WITH CLINICAL DEPARTMENTS

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 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 both 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 2017, analyses using this material have demonstrated the clinical relevance of results generated in more experimental systems.

Several clinical studies have been performed in patients wth coronary artery disease (CAD). In the HUNT study we have examined the association between inflammatory mediators and risk for myocardial infarction (MI) in healthy individuals. We have also performed interventional studies together with the Department of Cardiology with cytokine inhibitors in patients with MI.

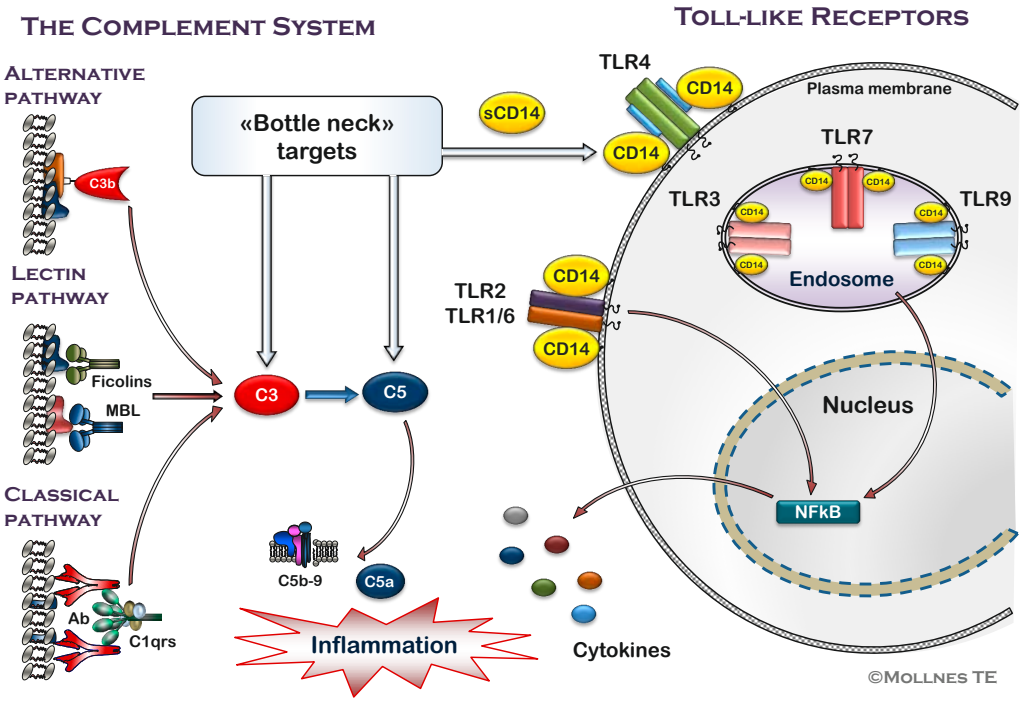
In inflammatory bowel disease (IBD) several clinically oriented projects, extensive studies have been done on biomarkers for IBD. A further development of clinical-basal collaboration is being implemented, with funding now approved for a research nurse who will administer inclusion and follow-up of IBD patients at the Day Unit of the Department of Gastroenterology.

In studies of pleeclampsia, CEMIR has been a part of the EU project InterPregGen, the first preeclampsia risk gene has been identified in the fetal genome. We have performed studies in a HUNT cohort of women with normal and preeclamptic pregnancies in close collaboration with the Women´s Clinic at Haukeland University Hospital.

Finally, 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, autophagy and IL-6 mediated cachexia.

INNOVATION STRATEGIES
FOR CONTROLLING INFLAMMATION

THE CONCEPT OF DUAL INHIBITION OF COMPLEMENT AND CD14



The "double blockade" of bottleneck recognition molecules at innate immune recognition. An upstream approach for inhibition of inflammation achieved by targeting the key complement molecules C3 or C5 and the CD14 molecule of the TLR family are proposed. Combined inhibition of these molecules will reduce the downstream inflammatory response substantially (Mollnes et al., J Leukoc Biol, 2017).

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 inflammation may also occur during ischemic/reperfusion that frequently happens in conjunction with infarction, trauma and transplantation. 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 the principle of "double -blockade" of complement and CD14 to attenuate inflammation (Figure 1). The principle was proposed and has been driven by one of the CEMIR researchers (TE Mollnes). Moreover, CEMIR researchers at NTNU (T Espevik et al) have developed the anti-CD14 antibody 18D11 that is effective in the combined treatment and currently is produced as a recombinant humanized antibody for therapeutic use. Three patents have been posted related to this project. A formal collaboration contract has been made with a company producing a C5 inhibitor for clinical use. The aim is to test this principle in clinical therapeutic settings in collaboration with Inven2 (the TTO at University of Oslo), and NTNU Technology Transfer AS. The project received grants from the BIOTEK program from The Research Council of Norway for the period 2015-2017. The other innovation strategy is to control inflammation by interfering with the Toll-like receptor 4 signaling pathway. We have identified interaction domains in two intracellular proteins that seem to be required to mount an inflammatory response towards Gram-negative bacteria. Based on these data we have propose to construct and optimize peptides that interfere with the interaction of these two proteins, and subsequently inhibit the inflammatory response. These anti-inflammatory peptides may form a new treatment strategy for preventing serious host reactions towards Gram-negative bacteriawich is being developed in collaboration with TTO at NTNU.

INTERNATIONAL COOPERATION

CEMIR has a comprehensive international network, and it is our goal to develop long-term international cooperation with excellent scientists and institutions. Six outstanding researchers have been appointed as adjunct professors at CEMIR since 2013, four of them from abroad:

Professor David Underhill, Cedars-Sinai medical Center, Los-Angeles, USA
Professor Katherine Fitzgerald, University of Massachusetts, USA
Professor Eicke Latz, University of Bonn, Germany
Professor Tom Eirik Mollnes, University of Oslo and University of Tromsø
Professor Egil Lien, University of Massachusetts, USA
Professor Harald Stenmark, University of Oslo

The adjunct professors are responsible for three PhD courses held yearly at NTNU: Advanced Cellular Imaging techniques, Receptor Signalling and Trafficking and Molecular Mechanisms of Inflammation. Further, the adjunct professors are co-supervising our PhD and postdoctoral candidates. Staff members are offered the possibility to spend extended periods in their laboratories. This is an important component of the researcher training, networking and internationalization of their research.

CEMIR has an international work environment - in 2017, 15 nationalities were represented in our staff. We also hosted a visiting researcher from Italy; A PhD candidate, Germana Lentini, from the lab of Professor Giuseppe Teti, University of Messina.

SOME EXPERIENCES FROM WORKING ABROAD:

Pontus Ørning (PhD),
UMass medical School (USA)

I'm a PhD candidate at NTNU working in the labs of Professors Egil Lien and Kate Fitzgerald at UMass Medical School in Massachusetts, USA, since 2014. I have been given a great opportunity to visit one of the leading universities in the field here at UMass. This research stay has made it possible for me to broaden my academic network and collaborate with renowned researchers helping to push the field forward. By living and working in Massachusetts I have gained access to some of the newest tools in the fields of CRISPR, deep sequencing and genome wide screens, as well as a huge variety of KO mouse strains, reagents and the most modern equipment and expertise that I can use for my own research.

Nathalie Niyonzima (Postdoc),
King's College London (Great Britain) and the National Institutes of Health (NIH) (USA)

I have had the opportunity to visit the former Kemper Lab in London for one year (2016), and to move with her to NIH (2017-2018). The research abroad is founded by the Norwegian Research Council FRIPO mobility grant. Both King's College and NIH have offered me a tremendous opportunity to establish connections with several labs that are experts in the field of Immunology. I have taken advantage in working closely with other labs and collaborators of the Kemper lab, and using their expertise for my research. This has given me the opportunity to participate in many formal and non-formal meetings across the many NIH campuses. It has also given me access to the most modern imaging and animal core facilities that have advanced my research to another level.

Marte Singsås Dragset (researcher)
Pujol Research Institute, Spain

I am a researcher working in the lab of Pere Joan Cardona at Germans Trias i Pujol Research Institute outside Barcelona, Spain since 2016. I am granted by Norwegian Research Council's FRIPRO Mobility Grant, which means that I will spend two years abroad before I return to CEMIR, NTNU, for a third year. I work with the interaction of host and pathogen, specifically I search for mycobacterial virulence genes important to establish infection. In the Cardona lab I get to work with Drosophila melanogaster (the common fruit fly) as a host, and I'm thrilled to get to know this historically important model organism.

CEMIR PHD DISSERTATION 2017
FOR THE DEGREE OF PHILOSOPHIA DOCTOR

Guro S. Stødle
defended her thesis "Pattern recognition receptor mediated inflammation in placental trophoblasts" on November 24, 2017 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 Ann-Charlotte Iversen, professor Rigmor Austgulen and senior adviser Merie Hjelmseth Aune as supervisors.

Jennifer Melanie Mildenberger
defended her thesis "The interplay of oxidative stress responses and autophagy in inflammation" on June 14, 2017 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 with Professor Geir Bjørkøy and Trude Helen Flo as supervisors.

The cake donated by the Department of Clinical and Molecular Medicine when CEMIR got funding for five more years.


DAGENS Medisin

Nyheter Debatt DM Arena DMTV

FORSKER PÅ GRAVIDE: Dette er forskningsgruppe for inflammasjon i svangerskap, kalt svangerskapsgruppen, ved CEMIR ved NTNU. Ann-Charlotte Iversen er nummer to fra venstre og stipendiat Gabriela Silva er nr tre fra venstre. Foto: Jacob S. Jensen

FORSKNING

Fant verdens første risiko-gen for svangerskapsforgiftning


NORSK FORSKERBRAGD:

Ditt eget immunforsvar kan utløse kronisk sykdom og ta liv

Norsk forskerbragd: Immunforsvaret kan drepe

/ 2580 visninger


Styrket tro på at omega-3 reduserer risikoen for utvikling av alvorlige sykdommer

Et for hissig immunforsvar er årsak til autoimmune sykdommer og mistenkes også i forbindelse med kreft og Alzheimers. NTNU-forskere har funnet ut hvordan omega-3 demper skadelige betennelsesreaksjoner.

Professor Geir Bjørkøy har ledet forskningen på virkningene av omega-3. FOTO: NTNU

CEMIR OUTREACH 2017

At CEMIR we aim to make the public aware of and understand our research on inflammation, and how our research can contribute to the development of new treatments and diagnostic tools. We are involved in many outreach activities.

Website: www.ntnu.edu/cemir

Media Highlights

In July, our research group on preeclampsia got a lot of attention both in science and in regular papers after a publication in Nature Genetics describing the world's first innate risk gene for preeclampsia in the fetus.

Geir Bjørkøy was interviewed on the radio programme "Norges glasset" to talk about his research in July. Bjørkøys research group on autophagy and oxidative stress defense, was promoted in the newspapaer "Adresseavisa" after a publication in Autophagy on how omega-3 is redusing the risk of developing serious illness.

The TV2 News channel visited CEMIR and interviewed Tom Erik Mollnes and Terje Espevik when Mollnes was going to receive the international KFJ research prize from Righshospitalet København. The prize was given for his work on cardiovascular disease and severe blood poinsoning.

Outreach highlights to the public

Kristian K. Starheim presented for the Norwegian Cancer society at the volunteering day in April. A famous exhibition, "Body Worlds vital", visited Trondheim summer 2017. Trude Helen Flo was invited to talk about inflammation at a "Body world" seminar. Therese Standal was invited to talk about multiple myeloma for the Norwegian Blood cancer society and about fat and cancer at The Knowledge town – Trondheim.

Blogs

In English:

- How does the body discover invading streptococci? Blogger: Birgitta Ehrnstrøm
- Can a sugar treat atherosclerosis? Blogger: Siril S. Bakke
- CEMIR researcher appointed Young Associate Investigator by NCMM. Blogger: NTNUmedicine
- Bacterial needle injections into host cells block immune responses. Blogger: Egil Lien

In Norwegian

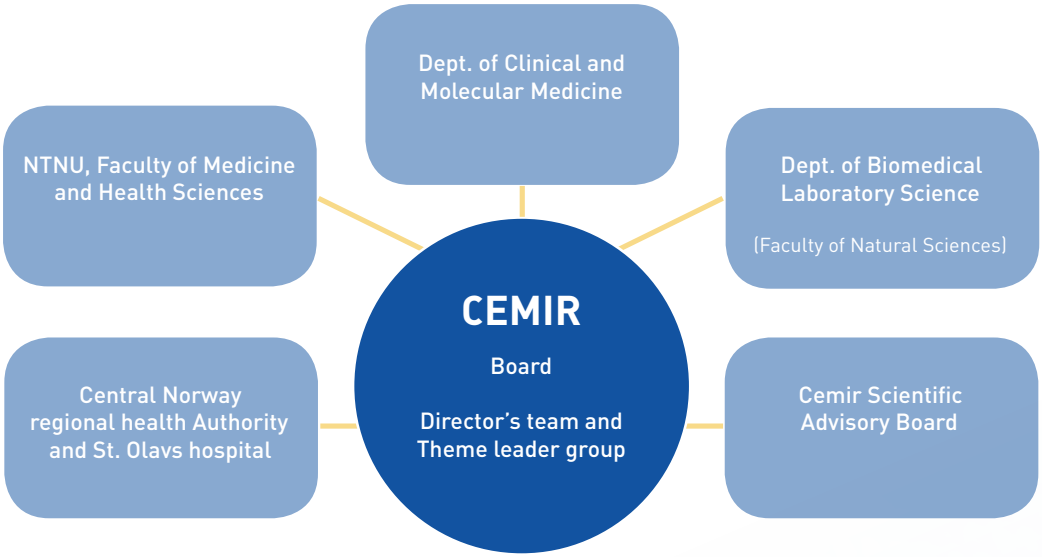
- Hvordan oppdager kroppen invaderende streptokokker? Blogger: Birgitta Ehrnstrøm
- Kan et sukker bekjempe aterosklerose? Blogger: Siril S. Bakke
- Bakterielle nåler gir blokkade av immunforsvaret Blogger: Egil Lien
- Immunterapi – Hjelp til sjølvhjelp. Blogger: Kristian K. Starheim

Blogs for the #NTNUmedicine blog from CEMIR: http://blog.medisin.ntnu.no/tag/cemir-en

Science sets Sail

Jenny Ostrop was invited to be part of an interdisciplinary crew of 30 scientists, including 6 immunologists, sailing the Baltic Sea on the three-mast schooner Thor Heyerdahl in August. Divided in three watches the crew learned to operate the ship and fought against sea-sickness. Handling the 15 sails, sometimes pulling with four persons on one dew, taught a lot about communication and team-work. Being on lookout or having galley (kitchen) duty together gave many opportunities to discuss intra- and inter-disciplinary research, in addition to an «Open Ship Day» dedicated to public science communication. It is to be hoped that the Science Sets Sail project initiated by FAU Erlangen-Nürnberg (Germany) will be repeated and further CEMIR scientists get a chance to participate.

ABOUT CEMIR



CEMIR is connected to the host department, 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 contribute 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 Sceince 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 6 international researchers employed as Professor II.

CEMIR board
One board meeting were held in 2017.

The board members are:
Magne Børset – (Board chairman) Head of Dep. of Cancer Research and Molecular Medicine, NTNU
Björn Gustafsson - Dean, Faculty of Medicine, NTNU
Terje Meisler - Dean, Faculty of Technology, NTNU
Petter Aadahl - Research director, St. Olavs Hospital
Anne Borg - Dean, Faculty of Natural Sciences and Technology, NTNU

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.

EVENTS AT CEMIR

«The CEMIR team reaches the top together»

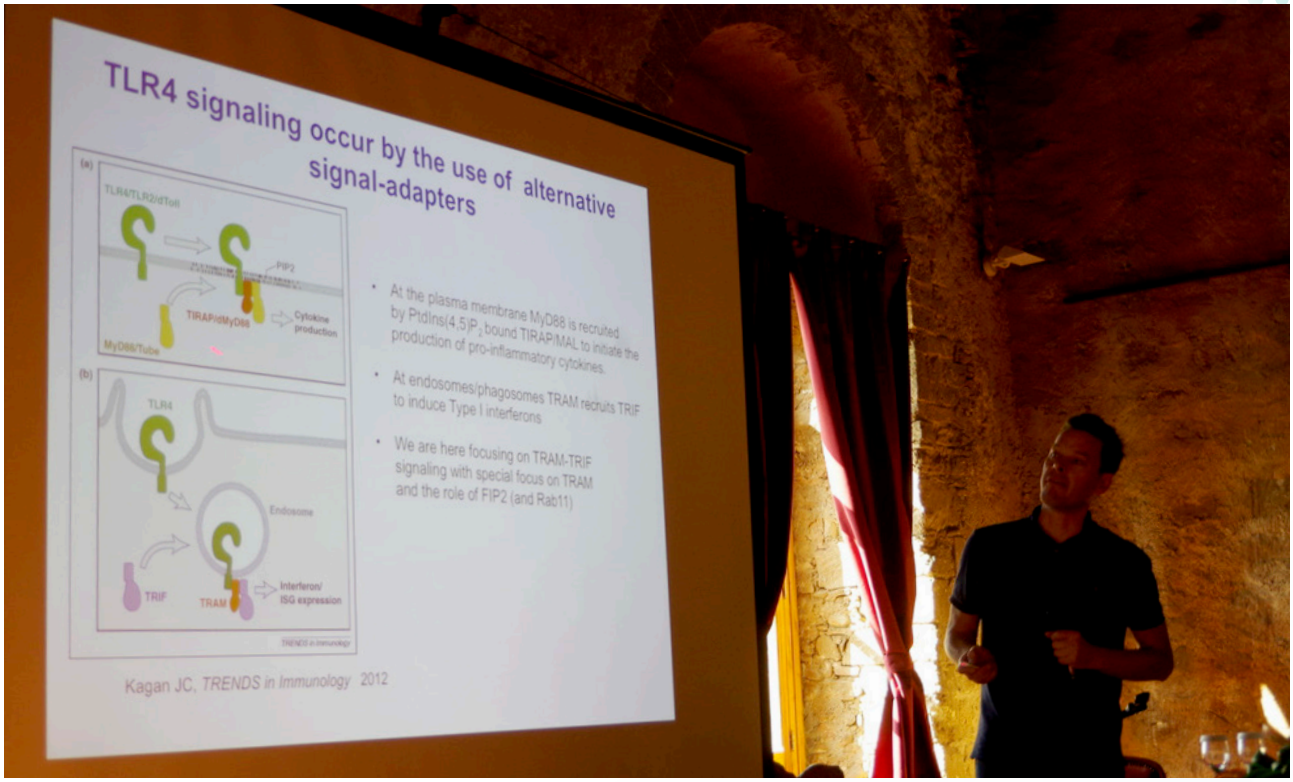
Taormina trip

In October 2017 CEMIR organized a retreat for their employees in Taormina, Sicily, Italy. This place was chosen because of the close scientific collaboration between CEMIR and professor Giuseppe Teti, University of Messina, Sicily, and he was the local organizer for the retreat. This retreat was a great scientific and social success and 60 employees participated.

We arrived at Taormina late monday night where we immediately met in the hotel restaurant for dinner. The next day we took the spectacular cable car to the old town in Taormina. In a venerable building with lots of history; Palazzo Duchi di Santo Stefano, we had a scientific seminar. A lunch packet was provided after the seminar and of we went on a fantastic guided trip to Etna. Back in Taormina at late night, we joined for a dinner in the old town.

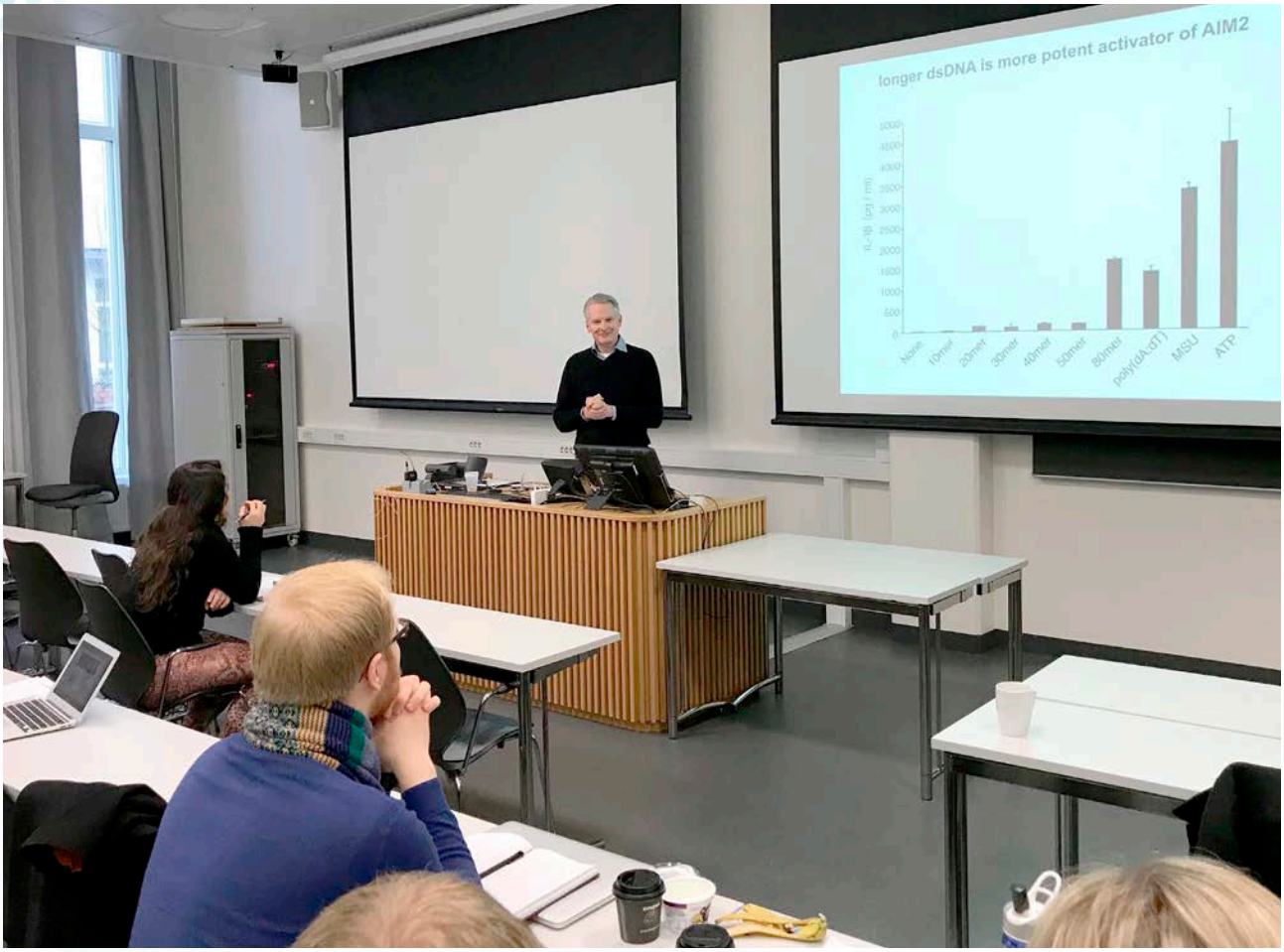
The following day was devoted to a scientific seminar together with some scientific fellows from the University of Messina. Our PhD students had the opportunity to present their research, and Prof. Espevik's longtime collaborator, Giò Teti from the University of Messina, Sicily, had a scientific talk. There was time allocated for group work, where we talked about the working environment at CEMIR and how to develop it. All groups presented their thoughts, and minutes were written to further work on back home. In the evening, we had a fantastic farewell dinner together with Giò Teti at the Excelsior Hotel making prof. Teti "The Viking of the Year".

On Thursday we went home with a lot of great impressions and new energy. Ready to take CEMIR to the top together.



Scientific talk by Harald Husebye at the Taormina retreat.

The long-time collaborator, Giò Teti (University of Messina, Sicily) is declared the "Viking of the year".



Prof. Eicke Latz giving a talk about «Remember your diet».

Guest lectures
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 to get scientific insight from excellent researchers from other universities.

April 26th Professor Boris Reizis, NYU School of Medicine, USA: "Innate mechanisms in systemic lupus erythematosus".

June 16th Associate Professor Elena Kashuba Karolinske Institutet, Sweden: «Role of the mitochondrial ribosomal protein S18-2 in cancerogenesis».

September 9th Martin Roelsagaards Jakobsen, Aarhus University, Denmark: "Novel innate immune regulation in macrophages and pDCs "

September 20th Prof. Keshava Prasad, Deputy Director, Center for Systems Biology and Molecular Medicine, Mangalore, India: "Functional proteomics and metabolomics to investigate molecular networks associated with human diseases ".

November 9th Prof. Egil Lien from University of Massachusetts and CEMIR/NTNU: «Activation and evasion of innate immunity: Lessons from highly virulent bacteria»

November 10th Prof. Tom Eirik Mollnes, University of Bergen and CEMIR/NTNU: «Dual inhibition of complement and CD14 - a future strategy to treat inflammation?»

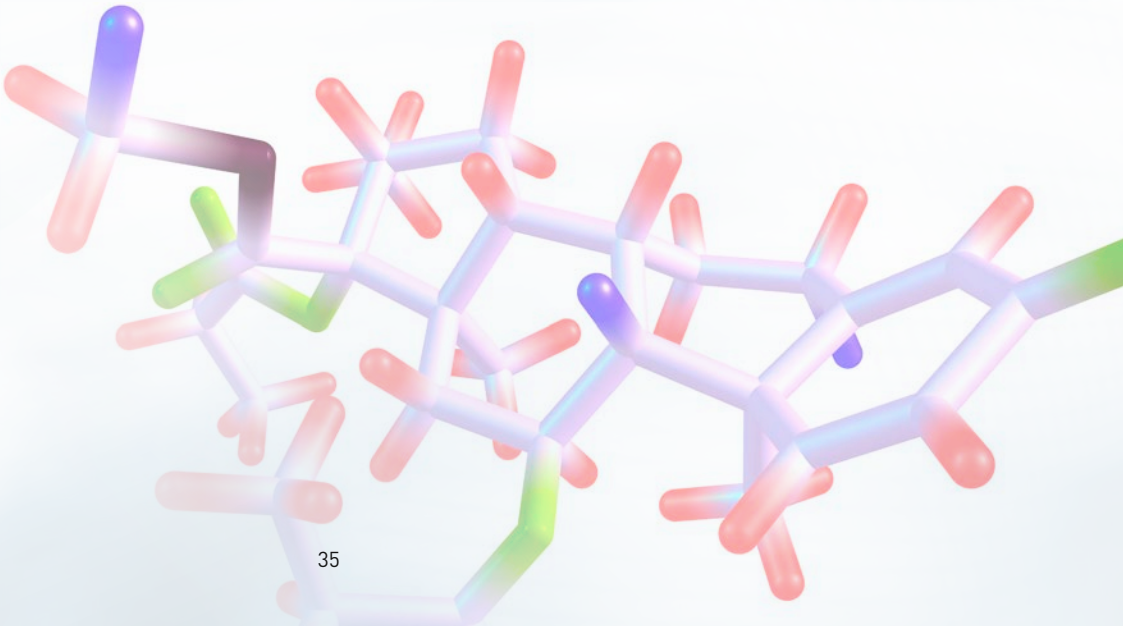
November 28th Prof Eicke Latz, University of Bonn and CEMIR/NTNU, Germany: «Remember your diet»

November 29th David Underhill Cedars-Sinai, USA: "A Role for the Fungal Microbiome in Crohn's Disease?"

Prizes, awards and appointments 2017

Tom Erik Mollnes – The KFJ Prize
The KFJ Prize of DKK 1.5 million is awarded annually by Rigshospitalet in Copenhagen and goes to an international researcher at a high level. This year the award was given to Professor Tom Eirik Mollnes, for research that can make it easier to treat cardiovascular disease and severe blood poisoning. Mollnes has previously developed a method for measuring the activity of our innate immune sys tem. Now, it is used as a default method worldwide. We congratulate Professor Mollnes with the prestigious award!

Richard Kumaran Kandasamy –
Appointed as a Young Associate Investigator by the Centre for Molecular Medicine Norway (NCMM)
Centre for Molecular Medicine Norway (NCMM) is an international biomedical research centre, with the overall objective of translating basic medical research into clinical practice. NCMM is a part of UiO's interdisciplinary focus on life sciences. A Selection Committee appointed candidates after careful evaluation. The final candidates were chosen based on their scientific excellence, translational merit and/or the ability to build networks that bridge from basic science to clinical medicine, compatibility with the NCMM mission and added value they could bring to NCMM. Nominations are made for three years and will be renewable. Congratulations!

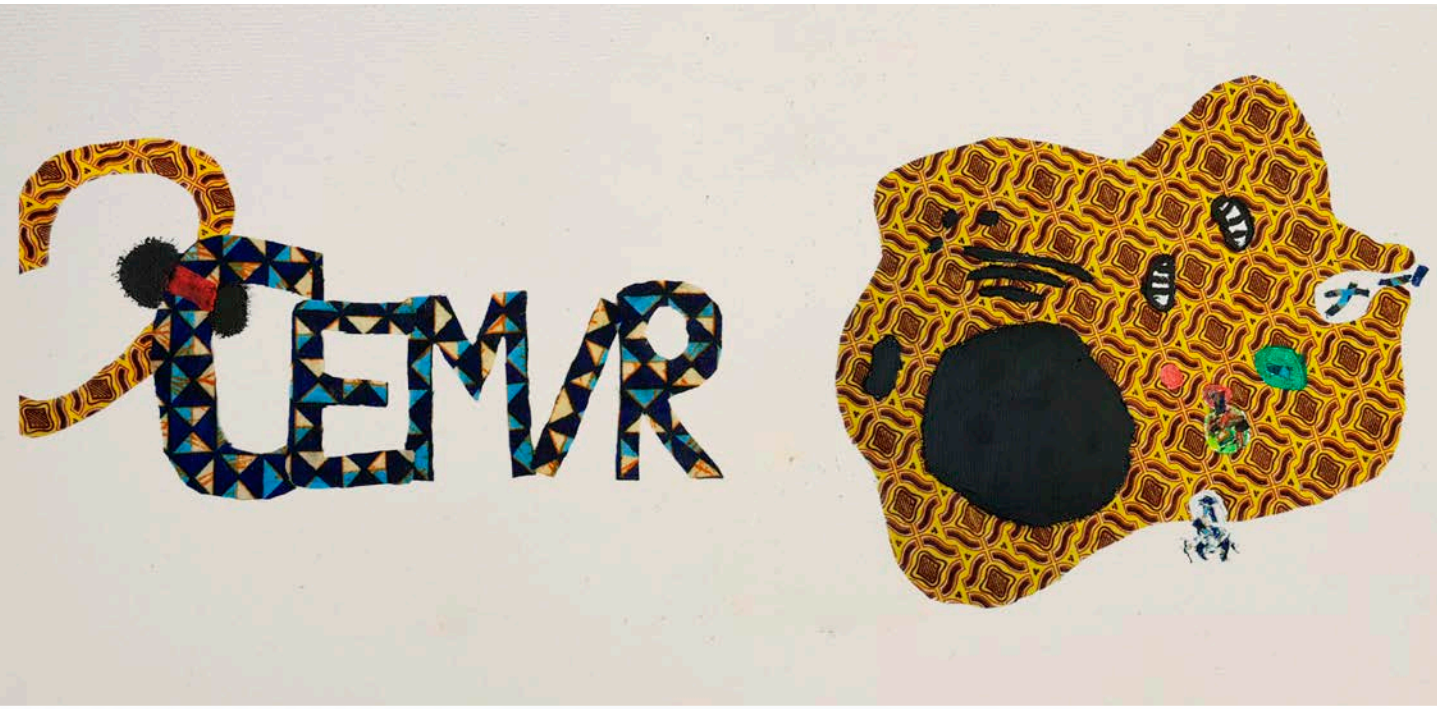


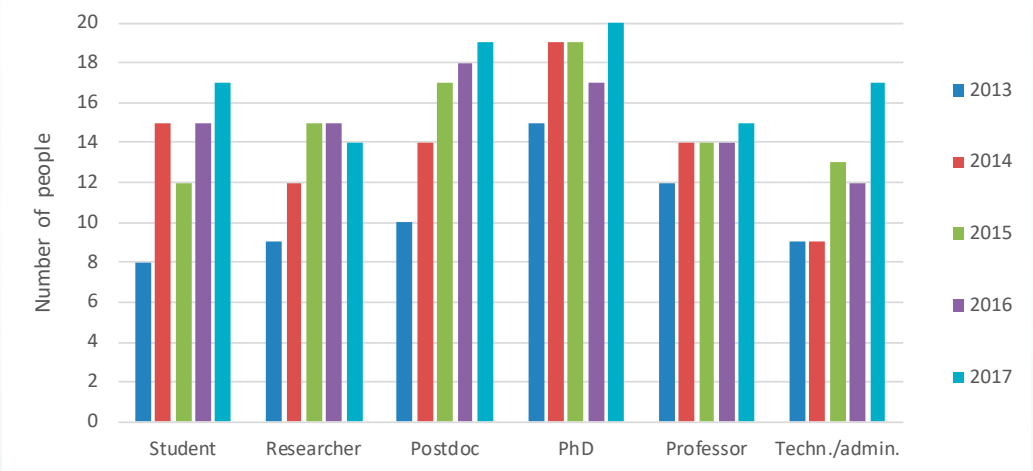
CEMIR staff and students

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 2017 68 scientific staff members, 16 technicians, 17 students and an administrative coordinator associated with the Centre.

GREETINGS FROM A FORMER EMPLOYEE. COLLAGE OF THE CEMIR LOGO AND THE CELL BY JANE AWUH





Name		Position	Nationality	Research group
Aas	Kristin	PhD candidate	Norway	Bone disease
Alonso	Mara	Postdoctor	Spain	Regeneration
Andersen	Sonja	Staff engineer	Norway	Autophagy
Awuh	Jane	Postdoctor	Cameroon	Mycobacteria & HIV
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 K	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
Grøvdal	Lene Melsæther	Researcher	Norway	Inflammation
Haug	Markus	Researcher	Norway	Mycobacteria & HIV
Husebye	Harald	Researcher	Norway	Inflammation
Ibrahim	Hany	PhD candidate	Egypt	Mycobacteria & HIV
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	
Lentini	Germana	PhD candidate	Italy	
Lien	Egil	Professor II	Norway	
Louet	Claire	Staff engineer	France	Mycobacteria & HIV
Marstad	Anne	Staff engineer	Norway	Mycobacteria & HIV
Moharrami	Neda Nejati	PhD candidate	Iran	Inflammation
Mollnes	Tom Eirik	Professor II	Norway	
Mundal	Siv Boon	PhD candidate	Norway	Pregnancy

Mærk	Mali	Postdoctor	Norway	Mycobacteria & HIV
Neckmann	Ulrike	PhD candidate	Germany	Autophagy
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
Paulsen	Julie	PhD candidate	Norway	Inflammation
Pettersen	Kristine	Postdoctor	Norway	Autophagy
Richard	Gabriel	Staff engineer	India	System Inflammation
Rokstad	Anne Mari	Researcher	Norway	Inflammation
Ryan	Liv	Staff engineer	Norway	Inflammation
Samstad	Eivind	Researcher	Norway	Inflammation
Sandvik	Arne	Professor	Norway	IBD
Serrre	Ignacio Katalan	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
Solberg	Morten	Researcher	Norway	
Spanjers	Roos	Scientific assistent	Netherlands	Regeneration
Sporsheim	Bjørnar	Staff engineer	Norway	
Standal	Therese	Professor	Norway	Bone disease
Starheim	Kristian K.	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
Sundan	Anders	Professor	Norway	Bone disease
Thorsvik	Silje	PhD candidate	Norway	IBD
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	
Østvik	Ann Elisabeth	Researcher	Norway	IBD
Åsberg	Signe	PhD candidate	Norway	Mycobacteria & HIV

RESULTS 2017:
Publications, theses and academic presentations

Awuh, Jane Atesoh; Flo, Trude Helen. Molecular basis of mycobacterial survival in macrophages. Cellular and Molecular Life Sciences (CMLS) 2017 s. 1–24

Bakke, Siril Skaret; Aune, Marie Hjelmseth; Niyonzima, Nathalie; Pilely, Katrine; Ryan, Liv; Skjelland, Mona; Garred, Peter; Aukrust, Pål; Halvorsen, Bente; Latz, Eicke; Damås, Jan Kristian; Mollnes, Tom Eirik; Espevik, Terje. Cyclodextrin Reduces Cholesterol Crystal-Induced Inflammation by Modulating Complement Activation.. Journal of Immunology 2017 ;Volum 199.(8) s. 2910–2920

Barratt-Due, Andreas; Pischke, Søren Erik; Nilsson, Per; Espevik, Terje; Mollnes, Tom Eirik. Dual inhibition of complement and Toll-like receptors as a novel approach to treat inflammatory diseases-C3 or C5 emerge together with CD14 as promising targets.. Journal of Leukocyte Biology 2017 ;Volum 101.(1) s. 193–204

Benet-Campos C, Cuéllar C, García-Ballesteros C, Zamora V, Gil-Borrás R, Catalán-Serra I, López-Chuliá F, Andreu-Ballester JC. Determination of Anti-Anisakis Simplex Antibodies and Relationship with αβ and γδ Lymphocyte Subpopulations in Patients with Crohn's Disease. Dig Dis Sci. 2017 Apr;62(4):934–943.

Braga, Tarcio Teodoro; Forni, Maria Fernanda; Correa-Costa, Matheus; Ramos, Rodrigo Nalio; Barbuto, Jose Alexandre; Branco, Paola; Castoldi, Angela; Hiyane, Meire Ioshie; Davanso, Mariana Rodrigues; Latz, Eicke; Franklin, Bernardo S.; Kowaltowski, Alicia J.; Camara, Niels Olsen Saraiva. Soluble Uric Acid Activates the NLRP3 Inflammasome. *Scientific Reports* 2017 ;Volum 7:39884. s. 1–14

Bugge, Marit; Bergstrøm, Bjarte; Eide, Oda K; Solli, Helene; Kjønstad, Ingrid Fadum; Stenvik, Jørgen; Espevik, Terje; Nilsen, Nadra J.. Surface Toll-Like Receptor 3 Expression in Metastatic Intestinal Epithelial Cells induces Selective Cytokine Production and Promotes Invasiveness. Journal of Biological Chemistry 2017; Volum 292.(37) s. 15408–15425

Catalan-Serra, Ignacio; Sandvik, Arne Kristian; Bruland, Torunn; Andreu-Ballester, Juan Carlos. Gammadelta T cells in Crohn's disease: a new player in the disease pathogenesis?. Journal of Crohn's and Colitis 2017 s. 1–11 HNT NTNU STO Ehrnstrøm, Birgitta; Beckwith, Kai Sandvold; Yurchenko, Mariya; Moen, Siv Helen; Kojen, June Frengen; Lentini, Germana; Teti, Guiseppe; Damås, Jan Kristian; Espevik, Terje; Stenvik, Jørgen. Toll-Like Receptor 8 Is a Major Sensor of Group B Streptococcus But Not Escherichia coli in Human Primary Monocytes and Macrophages. Frontiers in Immunology 2017; Volum 8.

Eide IA, Åsberg A, Svensson M, Ueland T, Mollnes TE, Hartmann A, Bjerve KS, Michelsen A, Aukrust P, Christensen JH, Schmidt EB, Jenssen T. Plasma Levels of Marine n-3 Fatty Acids Are Inversely Correlated With Proinflammatory Markers sTNFR1 and IL–6 in Renal Transplant Recipients. J Ren Nutr. 2017 May;27(3):161–168

Espada S, Stavik B, Holm S, Sagen EL, Bjerkeli V, Skjelland M, Dahl TB, Espevik T, Kanse S, Sandset PM, Skretting G, Halvorsen B. Tissue factor pathway inhibitor attenuates ER stress-induced inflammation in human M2-polarized macrophages. Biochem Biophys Res Commun. 2017 Sep 16;491(2):442–448.

Genster N, Østrup O, Schjalm C, Eirik Mollnes T, Cowland JB, Garred P. Ficolins do not alter host immune responses to lipopolysaccharide-induced inflammation in vivo. Sci Rep. 2017 Jun 20;7(1):3852.

Gidon, Alexandre; Åsberg, Signe; Louet, Claire; Ryan, Liv; Haug, Markus; Flo, Trude Helen. Persistent mycobacteria evade an antibacterial program mediated by phagolysosomal TLR7/8/MyD88 in human primary macrophages. PLoS Pathogens 2017 ;Volum 13.(8)

Gierman, Lobke; Pervaiz, Zahra; Silva, Gabriela; Stødle, Guro; Rakner, Johanne Johnsen; Elschot, Mattijs; Dahlberg, Unn; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Iversen, Ann-Charlotte. An inflammatory role for TLR3 in decidua and placenta of normal and preeclamptic pregnancies. Placenta 2017; Volum 57. s. 278

Gómez-Escudero J, Moreno V, Martín-Alonso M, Hernández-Riquer MV, Feinberg T, Colmenar Á, Calvo E, Camafeita E, Martínez F, Oudhoff MJ, Weiss SJ, Arroyo AG. E-cadherin cleavage by MT2-MMP regulates apical junctional signaling and epithelial homeostasis in the intestine. J Cell Sci. 2017 Dec 1;130(23):4013–4027.

Gravastrand, Caroline; Hamad, Shamal; Fure, Hilde; Steinkjer, Bjørg; Ryan, Liv; Oberholzer, José; Lambris, John D.; Lacík, Igor; Mollnes, Tom Eirik; Brekke, Ole-Lars; Rokstad, Anne Mari. Alginate microbeads are coagulation compatible, while alginate microcapsules activate coagulation secondary to complement or directly through FXII. Acta Biomaterialia 2017;Volum 58. s. 158–167

Gregersen I, Sandanger Ø, Askevold ET, Sagen EL, Yang K, Holm S, Pedersen TM,Skjelland M, Krohg-Sørensen K, Hansen TV, Dahl TB, Otterdal K, Espevik T, Aukrust P, Yndestad A, Halvorsen B. Interleukin 27 is increased in carotid atherosclerosis and promotes NLRP3 inflammasome activation. PLoS One. 2017 Nov 27;12(11):e0188387

Gustavsen A, Skattum L, Bergseth G, Lorentzen B, Floisand Y, Bosnes V, Mollnes TE, Barratt-Due A. Effect on mother and child of eculizumab given before caesarean section in a patient with severe antiphospholipid syndrome: A case report. Medicine (Baltimore). 2017 Mar;96(11):e6338.

Hansen, Marianne Dore; Johnsen, Ingvild Bjellmo; Stiberg, Kim Andre Ha; Sherstova, Tatyana; Wakita, Takaji; Richard, Gabriel Mary; Kandasamy, Richard Kumaran; Meurs, Eliane F.; Anthonsen, Marit Walbye. Hepatitis C virus triggers Golgi fragmentation and autophagy through the immunity-related GTPase M. Proceedings of the National Academy of Sciences of the United States of America 2017 ;Volum 114.(17) s. E3462–E3471

Harboe M, Johnson C, Nymo S, Ekholt K, Schjalm C, Lindstad JK, Pharo A, Hellerud BC, Nilsson Ekdahl K, Mollnes TE, Nilsson PH. Properdin binding to complement activating surfaces depends on initial C3b deposition. Proc Natl Acad Sci U S A. 2017 Jan 24;114(4):E534–E539.

Hellerud BC, Orrem HL, Dybwik K, Pischke SE, Baratt-Due A, Castellheim A, Fure H, Bergseth G, Christiansen D, Nunn MA, Espevik T, Lau C, Brandtzæg P, Nielsen EW, Mollnes TE. Combined inhibition of C5 and CD14 efficiently attenuated the inflammatory response in a porcine model of meningococcal sepsis. J Intensive Care. 2017 Feb 27;5:21.

Hennø LT, Storjord E, Christiansen D, Bergseth G, Ludviksen JK, Fure H, Barene S, Nielsen EW, Mollnes TE, Brekke OL. Effect of the anticoagulant, storage time and temperature of blood samples on the concentrations of 27 multiplex assayed cytokines – Consequences for defining reference values in healthy humans. Cytokine. 2017 Sep;97:86–95.

Holte E, Kleveland O, Ueland T, Kunszt G, Bratlie M, Broch K, Michelsen AE, Bendz B, Amundsen BH, Aakhus S, Damås JK, Gullestad L, Aukrust P, Wiseth R. Effect of interleukin-6 inhibition on coronary microvascular and endothelial function in myocardial infarction. Heart. 2017 Oct;103(19):1521–1527.

Hoss F, Rodriguez-Alcazar JF, Latz E. Assembly and regulation of ASC specks. Cell Mol Life Sci. 2017 Apr;74(7):1211–1229.

Keshari RS, Silasi R, Popescu NI, Patel MM, Chaaban H, Lupu C, Coggeshall KM, Mollnes TE, DeMarco SJ, Lupu F. Inhibition of complement C5 protects against organ failure and reduces mortality in a baboon model of Escherichia coli sepsis. Proc Natl Acad Sci U S A. 2017 Jul 18. pii: 201706818.

Labzin LI, Heneka MT, Latz E. Innate Immunity and Neurodegeneration. Annu RevMed. 2017 Nov 6.

Lunde, Ngoc Nguyen Dieu; Holm, Sverre; Dahl, Tuva Børresdatter; Inass, Elyouncha; Sporsheim, Bjørnar; Gregersen, Ida; Abbas, Azhar; Skjelland, Mona; Espevik, Terje; Solberg, Rigmor; Johansen, Harald Thidemann; Halvorsen, Bente. Increased levels of legumain in plasma and plaques from patients with carotid atherosclerosis. Atherosclerosis 2017 ;Volum 257. s. 216–223

McGinnis, Ralph; Steinthorsdottir, Valgerdur; Williams, Nicholas O.; Thorleifsson, Gudmar; Shooter, Scott; Hjartardóttir, Sigrún; Bumpstead, Suzannah; Stefánsdóttir, Lilja; Hildyard, Lucy; Sigurdsson, Jon K.; Kemp, John P.; Silva, Gabriela; Thomsen, Liv Cecilie Vestrheim; Jääskeläinen, Tiina; Kajantie, Eero; Chappell, Sally; Kalsheker, Noor; Moffett, Ashley; Hiby, Susan; Lee, Wai Kwong; Padmanabhan, Sandosh; Simpson, Nigel A.B.; Dolby, Vivien A.; Staines-Urias, Eleonora; Engel, Stephanie M.; Haugan, Anita; Trogstad, Lill; Svyatova, Gulnara; Zakhidova, Nodira; Najmutdinova, Dilbar; Dominiczak, Anna F.; Gjessing, Håkon K.; Casas, Juan P.; Dudbridge, Frank; Walker, James J.; Pipkin, Fiona Broughton; Thorsteinsdóttir, Unnur; Geirsson, Reynir Tõmas; Lawlor, Debbie A.; Iversen, Ann-Charlotte; Magnus, Per; Laivuori, Hannele; Stefánsson, Kári; Morgan, Linda. Variants in the fetal genome near FLT1 are associated with risk of preeclampsia. Nature Genetics 2017 ;Volum 49.(8) s. 1255–1260

Mehl, Arne; Åsvold, Bjørn Olav; Lydersen, Stian; Paulsen, Julie; Solligård, Erik; Damås, Jan Kristian; Harthug, Stig; Edna, Tom-Harald. Burden of bloodstream infection in an area of Mid-Norway 2002-2013: A prospective population-based observational study. BMC Infectious Diseases 2017 ;Volum 17:205. s. 1–14

Mehl A, Åsvold BO, Kümmel A, Lydersen S, Paulsen J, Haugan I, Solligård E, Damås JK, Harthug S, Edna TH. Erratum to: Trends in antimicrobial resistance and empiric antibiotic therapy of bloodstream infections at a general hospital in mid-Norway: a prospective observational study. BMC Infect Dis. 2017 Jun 23;17(1):446.

Mildenberger J, Johansson I, Sergin I, Kjøbli E, Damås JK, Razani B, Flo TH, Bjørkøy G. N-3 PUFAs induce inflammatory tolerance by formation of KEAP1-containing SQSTM1/p62-bodies and activation of NFE2L2. Autophagy. 2017 Oct 3;13(10):1664–1678.

Nilsson PH, Thomas AM, Bergseth G, Gustavsen A, Volokhina EB, van den Heuvel LP, Barratt-Due A, Mollnes TE. Eculizumab-C5 complexes express a C5a neoepitope in vivo: Consequences for interpretation of patient complement analyses. Mol Immunol. 2017 Sep;89:111–114.

Niyonzima, Nathalie; Halvorsen, Bente; Sporsheim, Bjørnar; Garred, Peter; Aukrust, Pål; Mollnes, Tom Eirik; Espevik, Terje. Complement activation by cholesterol crystals triggers a subsequent cytokine response. Molecular Immunology 2017 ;Volum 84. s. 43–50

Olsen, Oddrun Elise; Skjærvik, Anette; Størdal, Berit Fladvad; Sundan, Anders; Holien, Toril. TGF-ß contamination of purified recombinant GDF15. PLoS ONE 2017 ;Volum 12:e0187349.(11) s. 1–10

Ostrop, Jenny; Roland, Lang. Contact, Collaboration, Conflict: Signal Integration of Syk-coupled C-type Lectin Receptors. Journal of Immunology 2017 ;Volum 198.(4) s. 1403–1414

Paulsen, Julie; Askim, Åsa Susanne; Mohus, Randi Marie; Mehl, Arne; Dewan, Andrew; Solligård, Erik; Damås, Jan Kristian; Åsvold, Bjørn Olav. Associations of obesity and lifestyle with the risk and mortality of bloodstream infection in a general population: a 15-year follow-up of 64 027 individuals in the HUNT Study. International Journal of Epidemiology 2017 ;Volum 46.(5) s. 1573–1581

Paunas TIF, Finne K, Leh S, Marti HP, Mollnes TE, Berven F, Vikse BE. Glomerular abundance of complement proteins characterized by proteomic analysis of laser-captured micro-dissected glomeruli associates with progressive disease in IgA nephropathy. Clin Proteomics. 2017 Aug 14;14:30.

Pedersen, Tina Therese; Fenstad, Mona H.; Moksnes, Tone; Wallenius, Marianne; Flo, Trude Helen; Haug, Markus. Cytokines and lipocalin-2 in pregnant women with rheumatoid arthritis and systemic lupus erythematosus. *Annals of the Rheumatic Diseases* 2017 ;Volum 76. Suppl. 2 s. 223–224

Pettersen, Kristine; Andersen, Sonja Benedikte; Degen, simone; Tadini, Valentina; Grosjean, Joel; Hatakeyama, Shinji; Tesfahun, Almaz Nigatu; Moestue, Siver Andreas; Kim, Jana; Nonstad, Unni; Romundstad, Pål Richard; Skorpen, Frank; Sørhaug, Sveinung; Amundsen, Tore; Grønberg, Bjørn Henning; Strasser, Florian; Stephens, Nathan; Hoem, Dag; Molven, Anders; Kaasa, Stein; Fearon, Kenneth; Jacobi, Carsten; Bjørkøy, Geir. Cancer cachexia associates with a systemic autophagy-inducing activity mimicked by cancer cell-derived IL–6 trans-signaling. Scientific Reports 2017 ;Volum 7.(1) s. 1–16

Pischke SE, Gustavsen A, Orrem HL, Egge KH, Courivaud F, Fontenelle H, Despont A, Bongoni AK, Rieben R, Tønnessen TI, Nunn MA, Scott H, Skulstad H, Barratt-Due A, Mollnes TE. Complement factor 5 blockade reduces porcine myocardial infarction size and improves immediate cardiac function. Basic Res Cardiol. 2017 May;112(3):20

Próchnicki T, Latz E. Inflammasomes on the Crossroads of Innate Immune Recognition and Metabolic Control. Cell Metab. 2017 Jul 5;26(1):71–93.

Raiborg C, Schink KO, Stenmark H. Suppressing mTORC1 on the lysosome. EMBO J. 2017 Jul 3;36(13):1809–1810

Rakner, Johanne Johnsen; Gierman, Lobke; Silva, Gabriela; Stødle, Guro; Elschot, Mattijs; Dahlberg, Unn; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Iversen, Ann-Charlotte. An inflammatory role for NOD1 in decidua and placenta of normal and preeclamptic pregnancies. Placenta 2017; Volum 57. s. 235

Rao SV, Solum G, Niederdorfer B, Nørsett KG, Bjørkøy G, Thommesen L. Gastrin activates autophagy and increases migration and survival of gastric adenocarcinoma cells. BMC Cancer. 2017 Jan 21;17(1):68.

Ratner, Dmitry; Ørning, Mathias Pontus; Lien, Egil. Bacterial secretion systems and regulation of inflammasome activation. Journal of Leukocyte Biology 2017 ;Volum 101.(1) s. 165–181

Riise, Hilde Kristin Refvik; Sulo, Gerhard; Tell, Grethe S.; Igland, Jannicke; Nygård, Ottar; Vollset, Stein Emil; Iversen, Ann-Charlotte; Austgulen, Rigmor; Daltveit, Anne Kjersti. Incident coronary heart disease after Preeclampsia: Role of reduced fetal growth, preterm delivery, and parity. Journal of the American Heart Association 2017 ;Volum 6:e004158.(3) s. 1–13 FHI

Rustad, Even Holth; Coward, Eivind; Skytøen, Emilie R; Misund, Kristine; Holien, Toril; Standal, Therese; Børset, Magne; Beisvag, Vidar; Myklebost, Ola; Meza, Leonardo Zepeda; Hong, Yan Dai; Sundan, Anders; Waage, Anders. Monitoring multiple myeloma by quantification of recurrent mutations in serum. Haematologica 2017 ;Volum 102.(7) s. 1266-1272

Shahini N, Michelsen AE, Nilsson PH, Ekholt K, Gullestad L, Broch K, Dahl CP, Aukrust P, Ueland T, Mollnes TE, Yndestad A, Louwe MC. The alternative complement pathway is dysregulated in patients with chronic heart failure. Sci Rep. 2017 Feb 14;7:42532.

Shields KJ, Mollnes TE, Eidet JR, Mikkelsen K, Almdahl SM, Bottazzi B, Lyberg T, Manzi S, Ahearn JM, Hollan I. Plasma complement and vascular complement deposition in patients with coronary artery disease with and without inflammatory rheumatic diseases. PLoS One. 2017 Mar 31;12(3):e0174577.

Smedbråten, Julia; Sagedal, Solbjørg; Åsberg, Anders; Hartmann, Anders; Rollag, Halvor; Mjøen, Geir; Fagerland, Morten; Hansen, S. W. K.; Mollnes, Tom Eirik; Thiel, S.. Collectin liver 1 and collectin kidney 1 of the lectin complement pathway are associated with mortality after kidney transplantation. American Journal of Transplantation 2017 ;Volum 17.(1) s. 265–271

Sokolova, Marina; Vinge, Leif Erik; Alfsnes, Katrine; Olsen, Maria Belland; Eide, Lars; Kaasbøll, Ole Jørgen; Attramadal, Håvard; Torp, May-Kristin; Fosshaug, Linn Elisabeth Lillerud; Rashidi, Azita; Lien, Egil; Finsen, Alexandra; Sandanger, Øystein; Aukrust, Pål; Ranheim, Trine; Yndestad, Arne. Palmitate promotes inflammatory responses and cellular senescence in cardiac fibroblasts. Biochimica et Biophysica Acta – Molecular and Cell Biology of Lipids 2017 ;Volum 1862.(2) s. 234–245

Solligård E, Damås JK. SOFA criteria predict infection-related in-hospital mortality in ICU patients better than SIRS criteria and the qSOFA score. Evid Based Med. 2017 Dec;22(6):211.

Starheim, Kristian K.; Kalvik, Thomas Vikestad; Bjørkøy, Geir; Arnesen, Thomas. Depletion of the human N-terminal acetyltransferase hNaa30 disrupts Golgi integrity and ARFRP1 localization. Bioscience Reports 2017 ;Volum 37:BSR20170066. (2) s. 1–11

Stavik B, Holm S, Espada S, Iversen N, Sporsheim B, Bjerkeli V, Dahl TB, Sandset PM, Skjelland M, Espevik T, Skretting G, Halvorsen B. Increased expression of TFPI in human carotid stenosis. Thromb Res. 2017 Jul;155:31-37.

Storjord, Elin; Dahl, Jim André; Landsem, Anne; Fure, Hilde; Ludviksen, Judith K; Goldbeck-Wood, Sandy; Karlsen, Bård Ove; Berg, Kristin Sandal; Mollnes, Tom Eirik; Nielsen, Erik Waage; Brekke, Ole Lars. Systemic inflammation in acute intermittent porphyria:a case–control study. Clinical and Experimental Immunology 2017 ;Volum 187.(3) s. 466–479

Stødle, Guro; Silva, Gabriela; Tangerås, Line Haugstad; Gierman, Lobke; Nervik, Ingunn; Dahlberg, Unn; Sun, Chen; Aune, Marie Hjelmseth; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Iversen, Ann-Charlotte. Inflammation in preeclampsia by NOD-like receptor protein (NLRP)3 inflammasome activation in trophoblasts. Pregnancy Hypertension 2017 ;Volum 9. s. 21

Thorsvik, Silje; Damås, Jan Kristian; Granlund, Atle van Beelen; Flo, Trude Helen; Bergh, Kåre; Østvik, Ann Elisabet; Sandvik, Arne Kristian. Fecal neutrophil gelatinase-associated lipocalin as a biomarker for inflammatory bowel disease. Journal of Gastroenterology and Hepatology 2017 ;Volum 32.(1) s. 128–135

Tyvold SS, Dahl T, Dragsund S, Gunnes S, Lyng O, Damås JK, Aadahl P, Solligård E. Bronchial microdialysis monitoring of inflammatory response in open abdominal aortic aneurysm repair; an observational study. Physiol Rep. 2017 Jul;5(14).

Ueland T, Laugsand LE, Vatten LJ, Janszky I, Platou C, Michelsen AE, Damås JK, Aukrust P, Åsvold BO. Monocyte/macrophage and T cell activation markers are not independently associated with MI risk in healthy individuals – results from the HUNT Study. Int J Cardiol. 2017 Sep 15;243:502-504.

Ueland T, Laugsand LE, Vatten LJ, Janszky I, Platou C, Michelsen AE, Damås JK, Aukrust P, Åsvold BO. Extracellular matrix markers and risk of myocardial infarction: The HUNT Study in Norway. Eur J Prev Cardiol. 2017 Jul;24(11):1161–1167.

Vaithilingam V, Steinkjer B, Ryan L, Larsson R, Tuch BE, Oberholzer J, Rokstad AM. In Vitro and In Vivo Biocompatibility Evaluation of Polyallylamine and Macromolecular Heparin Conjugates Modified Alginate Microbeads. Sci Rep. 2017 Sep 15;7(1):11695.

Vange P, Bruland T, Doseth B, Fossmark R, Sousa MML, Beisvag V, Sørdal Ø, Qvigstad G, Waldum HL, Sandvik AK, Bakke I. The cytoprotective protein clusterin is overexpressed in hypergastrinemic rodent models of oxyntic preneoplasia and promotes gastric cancer cell survival. PLoS One. 2017 Sep 13;12(9):e0184514.

Wheeler ML, Limon JJ, Underhill DM. Immunity to Commensal Fungi: Detente and Disease. Annu Rev Pathol. 2017 Jan 24;12:359–385.

Wibroe PP, Anselmo AC, Nilsson PH, Sarode A, Gupta V, Urbanics R, Szebeni J, Hunter AC, Mitragotri S, Mollnes TE, Moghimi SM. Bypassing adverse injection reactions to nanoparticles through shape modification and attachment to erythrocytes. Nat Nanotechnol. 2017 Jul;12(6):589–594.

Wolf-Grosse, Susann; Rokstad, Anne Mari; Ali, Syed; Lambris, JD; Mollnes, Tom Eirik; Nilsen, Asbjørn Magne; Stenvik, Jørgen. Iron oxide nanoparticles induce cytokine secretion in a complement-dependent manner in a human whole blood model. International Journal of Nanomedicine 2017 ;Volum 12. s. 3927–3940

Zahoor, Muhammad; Westhrin, Marita; Aass, Kristin Roseth; Moen, Siv Helen; Misund, Kristine; Psonka-Antonczyk, Katarzyna Maria; Giliberto, Mariaserena; Buene, Glenn; Sundan, Anders; Waage, Anders; Sponaas, Anne-Marit; Standal, Therese. Hypoxia promotes IL-32 expression in myeloma cells, and high expression is associated with poor survival and bone loss. Blood Advances 2017 ;Volum 27.(1) s. 2656–2666

Ziauddin SM, Yoshimura A, Montenegro Raudales JL, Ozaki Y, Higuchi K, Ukai T, Kaneko T, Miyazaki T, Latz E, Hara Y. Crystalline structure of pulverized dental calculus induces cell death in oral epithelial cells. J Periodontal Res. 2017 Nov 20.

Thesis

Mildenberger, Jennifer M. The interplay of oxidative stress responses and autophagy in inflammation. NTNU 2017

Stødle, Guro S. Pattern recognition receptor mediated inflammation in placental trophoblasts. NTNU 2017

Academic presentations

Beckwith, Marianne; Beckwith, Kai Sandvold; Strand, Trine Aakvik; Flo, Trude Helen.
In situ imaging of pyroptosis caused by Mycobacterium tuberculosis. Keystone X5: From Innate Immunity to Inflammatory Disease; 2017-03-19 - 2017-03-23

Bösl, Korbinian; Colinge, Jacques; Superti-Furga, Giulio; Snijder, Berend; Kandasamy, Richard Kumaran. Critical Nodes of Viral Modulation revealed through an Integrated Network Analysis of Host-Virus Interaction Landscape. Annual Meeting of the German Society for Immunology; 2017-09-12 - 2017-09-15

Bösl, Korbinian; Ibrahim, Hany; Richard, Gabriel Mary; Giambelluca, Miriam; Haug, Markus; Flo, Trude Helen; Kandasamy, Richard Kumaran. Integrative analysis of the inflammatory signalling kinome landscape CRISPR/Cas9-based genetic screens for identification of viral host factors. CSAMA 2017; 2017-06-11 - 2017-06-16

Bösl, Korbinian; Røst, Lisa Marie; Giambelluca, Miriam; Bruheim, Per; Kandasamy, Richard Kumaran. Integrative analysis of the inflammatory signalling kinome landscape. Digital Life 2017; 2017-03-20 - 2017-03-21

Bugge, Marit; Bergstrøm, Bjarte; Oda Kamilla, Eide; Solli, Helene; Kjønstad, Ingrid Fadum; Stenvik, Jørgen; Espevik, Terje; Nilsen, Nadra.
Surface Toll-Like Receptor 3 Expression in Metastatic Intestinal Epithelial Cells induces Inflammatory Cytokine Production and Promotes Invasiveness. Development of Tissue- and Pathogen-specific Cellular Innate Immunity; 2017-09-27 - 2017-09-29

Coward, Eivind; Misund, Kristine; Hofste op Bruinink, Davine; Hoogenboezem, Remco; Rustad, Even Holth; Myklebost, Ola; Sundan, Anders; Sonneveld, Pieter; Waage, Anders. Exome sequencing of multiple myeloma at sequential time points. Trondheim - Oslo Genome Dynamics Workshop; 2017-06-15 - 2017-06-16

Dragset, Marte Singsås. Screening for Mycobacterial Virulence Genes by Transposon Insertions Sequencing. MycoZAR 2017; 2017-09-28 - 2017-09-29

Espevik, Terje. Innate immunity – an overview. Rikshospitalet, University of Copenhagen. 22.01.2017

Espevik, Terje. Toll-like receptors and inflammasomes. Rikshospitalet, University of Copenhagen. 23.01.2017

Espevik, Terje. CD150 positively regulates TRAM recruitment to E. coli phagosomes and type I IFN secretion. Keystone symposia on Molecular and Cellular Biology, March 19-23, Banff, Alberta Canada.

Espevik, Terje. Complement, inflammasome activation and atherosclerosis. 16th European Meeting on Complement in Human Disease, September 08– 12, 2017

Espevik, Terje; Niyonzima, Nathalie; Bakke, Siril Skaret; Halvorsen, Bente; Gregersen, Ida; Skjelland, Ida; Yndestad, Arne; Sandanger, Øystein; Andersen, Geir Øystein; Gullestad, Lars; Latz, Eicke; Aukrust, Pål; Mollnes, Tome Eirik.
Systemic- and local complement activation controls the NLRP3 inflammasome pathway in patients with atherosclerosis. Lecture; 2017-09-09 - 2017-09-12

Flo, Trude Helen; Beckwith, Marianne; Beckwith, Kai Sandvold. The cell biology of Mycobacterium tuberculosis induced inflammasome activation and killing of host macrophages. The 35th annual meeeting Norwegian Society for Immunology; 2017-11-17

Flo Trude H; Espevik, Terje. Betennelse – et tveegget sverd for helse og sykdom. Seminar: «Fremragende søker fremragende» NTNU, 18. april.

Gidon, Alexandre. Persistent mycobacteria evade an antibacterial program mediated by phagolysosomal TLR7/8/MyD88 in human primary macrophages. 10th International Conference on the Pathogenesis of Mycobacterial Infections; 2017-08-23 - 2017-08-25

Gidon, Alexandre; Åsberg, Signe; Louet, Claire; Ryan, Liv; Haug, Markus; Flo, Trude Helen. Persistent mycobacteria evade an antibacterial program mediated by phagolysosomal TLR7/8/MyD88 in human primary macrophages.. Pattern Recognition Signaling: From Innate Immunity to Inflammatory Disease (X5); 2017-03-18 - 2017-03-24

Gierman, Lobke; Pervaiz, Zahra; Silva, Gabriela; Stødle, Guro; Rakner, Johanne Johnsen; Elschot, Mattijs; Dahlberg, Unn; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Iversen, Ann-Charlotte. An inflammatory role for TLR3 in decidua and placenta of normal and preeclamptic pregnancies. The IFPA Meeting; 2017-08-30 - 2017-09-02

Haug, Markus; Ibrahim, Hany; Kumashie, Kingsley; Flo, Trude Helen. Analysis of autophagy in activated primary human CD4+T cells under hypoxic conditions. IMMUNOLOGY 2017 (Annual Meeting of The American Association of Immunologists); 2017-05-12 - 2017-12-16

Ibrahim, Hany; Haug, Markus; Flo, Trude Helen. HIV infection - How inflammation matters. Global health seminar Autumn 2017; 2017-11-30 - 2017-11-30

Ibrahim, Hany; Kumashie, Kingsley; Flo, Trude Helen; Haug, Markus. Flow-cytometric analysis of autophagy in activated primary human CD4+ T cells under hypoxic conditions. NBS Contact Meeting 2017; 2017-02-19 - 2017-02-22

Kandasamy, Richard Kumaran. Decoding therapeutic targets of infectious diseases through systems–level approaches. Invited lecture; 2017-07-08 - 2017-07-08

Kandasamy, Richard Kumaran. Integrative systems-level approaches to study innate immunity. Invited lecture; 2017-02-08 - 2017-02-08

Mildenberger, Jennifer; Johansson, Ida; Kjøbli, Eli; Damås, Jan Kristian; Flo, Trude Helen; Bjørkøy, Geir. N-3 PUFAs induce inflammatory tolerance by formation of KEAP1 containing p62-bodies. ER Stress, Autophagy & Immune System.; 2017-01-26 - 2017-01-27

Misund, Kristine; Hofste op Bruinink, Davine; Coward, Eivind; Hoogenboezem, Remco; Rustad, Even Holth; Hovig, Eivind; Sundan, Anders; Myklebost, Ola; Sonneveld, Pieter; Waage, Anders. Detection of mutations in Multiple Myeloma during different stages of disease. NMSG plenary meeting; 2017-09-07 - 2017-09-08

Mærk, Mali. Development of an EsxG detection assay. JPIAMR noTBsec Project Meeting; 2017-02-26 – 2017-02-28

Olsen, Oddrun Elise; Sankar, Meenu; Darvekar, Sagar; Misund, Kristine; Sundan, Anders; Holien, Toril. Activins induce apoptosis through wild type ALK2/ACVR1 and are counteracted by BMPR2. The TGFb Superfamily: Signaling in Development and Disease; 2017-07-09 - 2017-07-14

Ostrop, Jenny. Central role of FcR as adaptor for innate immune receptors on myeloid cells. NBS Oppdalsmøte; 2017-03-22 – 2017-07-23

Ostrop, Jenny. Screening of organoid cultures to test effects of potential therapeutics on antimicrobial functions and tissue regeneration in the intestine. EMBL Course Bioimage Data Analysis - workflow session; 2017-05-17 – 2017-05-17

Ostrop, Jenny. The fascinating immune system at Open Ship Day of Science Sets Sail Project (http://science-sets-sail.fau.eu/about-the-project/). FAU Science Sets Sail; 2017-08-02 – 2017-08-09

Ostrop, Jenny; Kerntke, Christina; Gullik Sørbø, Håvard; Jozefowski, Katrin; Hupfer, Thomas; Louet, Claire; Gidon, Alexandre; Lepenies, Bernd; Flo, Trude Helen; Lang, Roland; Oudhoff, Menno. FcR is a central adaptor subunit for immune receptors on myeloid cells. EMBL course Bioimage Data Analysis - poster session; 2017-05-14 – 2017-05-14

Ostrop, Jenny; Kerntke, Christina; Gullik Sørbø, Håvard; Spanjers, Roos; Louet, Claire; Gidon, Alexandre; Lang, Roland; Flo, Trude Helen; Oudhoff, Menno. FcR is a central adaptor subunit for immune receptors on human macrophages. Annual Meeting of German Society for Immunology; 2017-09-12 – 2017-09-15

Ostrop, Jenny; Martin Alonso, Mara; Zwiggelaar, Rosalie; Spanjers, Roos; Arrowsmith, Cheryl H; Oudhoff, Menno. Semi-automated screening of organoid cultures to test effects of potential therapeutics on antimicrobial functions and tissue regeneration in the intestine. Annual Meeting of German Society for Immunology; 2017-09-12 – 2017-09-15

Rakner, Johanne Johnsen; Gierman, Lobke; Silva, Gabriela; Stødle, Guro; Elschot, Mattijs; Dahlberg, Unn; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Iversen, Ann-Charlotte. An inflammatory role for NOD1 in decidua and placenta of normal and preeclamptic pregnancies. The IFPA Meeting; 2017-08-30 – 2017-09-02

Skjesol, Astrid; Yurchenko, Mariya; Espevik, Terje; Husebye, Harald. The TLR4 adaptor TRAM controls phagocytosis of Gram-negative bacteria through interaction with the Rab11-family interacting protein 2. Type I Interferon: Friend and Foe Alike (X6); 2017-03-19 – 2017-03-23

Standal, Therese. Newer aspects of the bone disease in multiple myeloma. Nordic Myeloma Study Group Plenary Autumn Meeting; 2017-09-07 – 2017-09-08

Steigedal, Magnus. Role of Type VII-secretion in mycobacterial iron uptake. Gjesteforelesning University of Wurzburg; 2017-04-25 – 2017-04-25

Steigedal, Magnus; Mærk, Mali; Strand, Trine Aakvik. noTBsec: New intervention strategy for tuberculosis: blocking multiple essential targets. Early Discovery of new antibiotics; 2017-01-12 – 2017-01-13

Steigedal, Magnus; Mærk, Mali; Strand, Trine Aakvik. noTBsec New intervention strategy for tuberculosis: blocking multiple essential targets. TTA - Turning the Tide of Antimicrobial resistance; 2017-04-27 – 2017-04-28

Stødle, Guro; Silva, Gabriela; Tangerås, Line Haugstad; Nervik, Ingunn; Dahlberg, Unn; Sun, Chen; Aune, Marie Hjelmseth; Thomsen, Liv Cecilie Vestrheim; Bjørge, Line; Iversen, Ann-Charlotte. Inflammation in preeclampsia by NOD-like receptor protein (NLRP)3 inflammasome activation in trophoblasts. ISSHP European Congress; 2017-09-06 – 2017-09-09

Sulheim, Einar; Iversen, Tore Geir; To, Vu; Klinkenberg, Geir; Sletta, Håvard; Schmid, Ruth; Hatletveit, Anne Rein; Wågbø, Ane Marit; Sundan, Anders; Skotland, Tore; Sandvig, Kirsten; Mørch, Yrr Asbjørg. Cytotoxicity of Poly (alkyl cyanoacrylate) Nanoparticles. Controlled Release Society meeting; 2017-07-22 – 2017-07-24

Funding and Expenditures 2017

Funding (1000 NOK)	2017
NTNU	23 469
Research Council of Norway (RCN) – Centre of Excellence grant	21 147
Other RCN funding	8 787
Other public funding	19 168
Other private funding	3 056
Total funding	**75 627**

Expenditures (1000 NOK)	2017
Personnel and indirect costs	59 958
Equipment	286
Other operating costs	15 383
Total expenditures	**75 627**

Photo:
Page 3, 4, 7, 8,10, 11: Geir Mogen
Page 22, 23 (Richard Kandasamy): Hany Meås
Page 23 (upper photo): Adresseavisa
Page 12,15,16,17,18,19, 23 (two pictures at the bottom of the page), 25: Jacob Storgaard Jensen
Page 20, 21, 30 (bottom page, right side), 32,33 (bottom page): Janne Østvang
Page 28 (cake photo), 34: Terje Espevik
Page 32 (bottom page left side): Bjørg Steinkjer
Page 30, 33 (top photo): Jenny Ostrop
Page 35 (Tom Erik Mollnes): Kjartan Egeberg
Page 32 (top picture): Siril Bakke

Back cover photo made by Bjørg Steinkjer
CEMIR staff getting inspired by the Alcantra Gorge (Etna) in Sicily

HELSE MIDT-NORGE

ST. OLAVS HOSPITAL
TRONDHEIM UNIVERSITY HOSPITAL

NTNU
Norwegian University of
Science and Technology