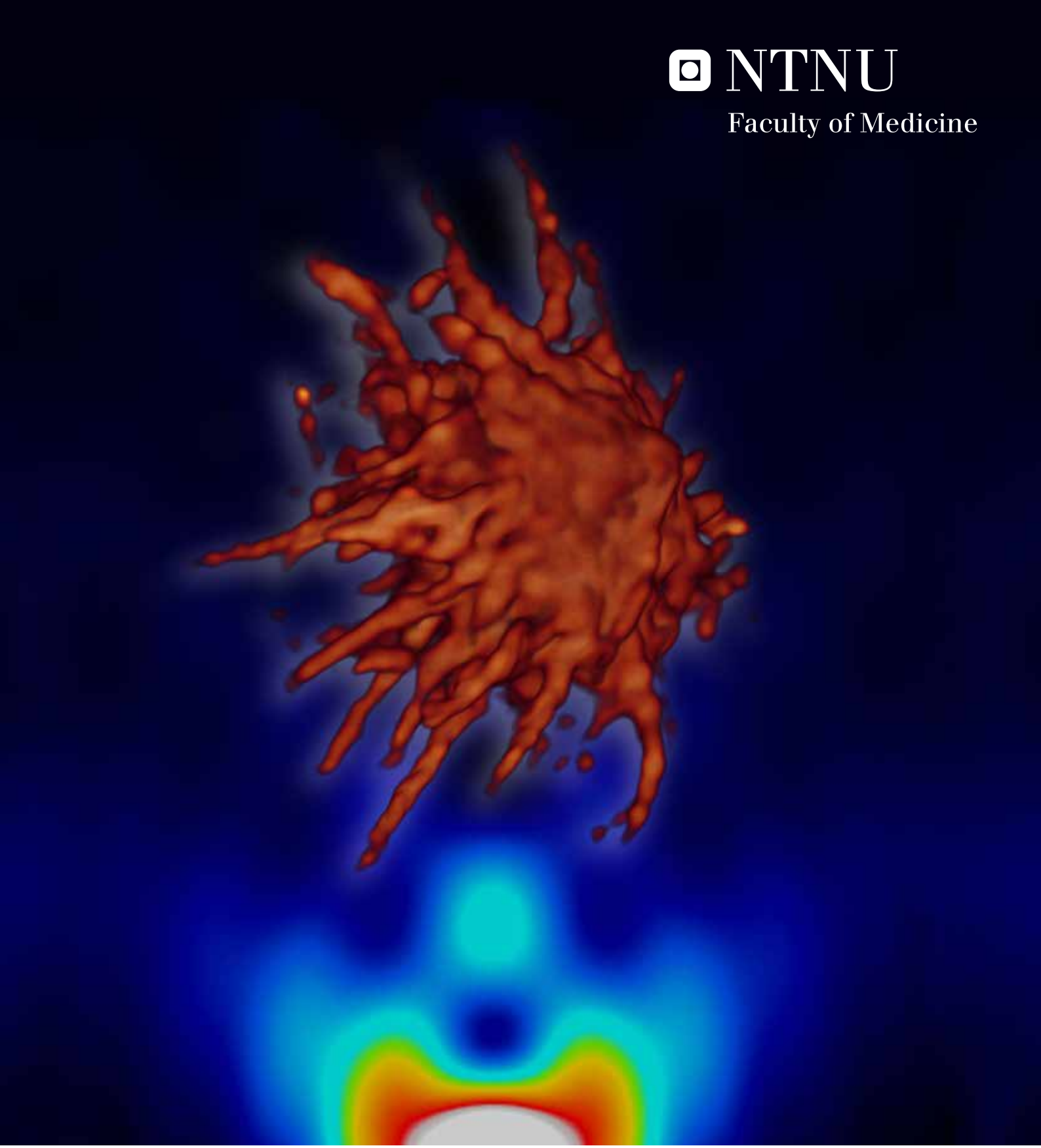
NTNU
Faculty of Medicine



CEMIR
Centre of Molecular Inflammation Research

Annual Report 2014

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Cover photo made by Bjørnar Sporsheim: Cover photo made by Bjørnar Sporsheim and Kjartan W. Egeberg: The image shows a 3-D volumetric representation of a live ASC speck inflammasome, consisting of 31 optical sections acquired on a Confocal Laser Scanning Microscope (CLSM) and deconvolved in Huygens Professional. Immortalized murine macrophages expressing mCerulean-ASC were stimulated with Nigericin in order to induce formation of ASC speck inflammasomes (approx. 8 micrometer) in the cytoplasm. In the background is a part of an axial (Z-axis) cross section of a computer-generated point spread function (PSF) calculated based on a 1.4 NA oil immersion objective at 520 nm emission. The PSF is a critical component in the deconvolution process, which mathematically re-assigns out-of-focus light back to its original focus point, thus increasing image quality and resolution.

DIRECTOR'S COMMENT

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

Inflammation is a host response that is triggered by noxious stimuli arising during infection and tissue injury. A controlled inflammatory response is needed to fight infections and to heal wounds, but can become detrimental if dysregulated. CEMIR performs basic and clinical inflammation research, and our aim is to unite scientists across disciplines for breaking new grounds in inflammation research.

CEMIR was established as a Centre of Excellence January 1, 2013. By the end of 2014 59 scientific staff members, 8 technicians and 15 students were associated with the centre. Since June 2014 CEMIR research activities have been located in the new Knowledge Centre at Øya Campus in Trondheim, owned by St. Olavs Hospital and NTNU. The Knowledge Centre hosts first-class laboratories with state of the art cellular imaging instruments, and it is a great advantage for CEMIR having easy access to these facilities and other laboratories in neighboring centres. CEMIRs' location at the university hospital also facilitates research cooperation with the clinicians and the important translational research on human disease.

We have an international work environment with 20 countries represented in our staff. Six outstanding national and international researchers are employed as adjunct professors at CEMIR. Three of our PhD students and two Post doctors were visiting our international collaborators in 2014 (at University of Massachusetts, Cedars-Sinai Medical Center, University of Bonn and University of Oslo). The national and international adjunct professors are responsible for three PhD courses held yearly at CEMIR: *Advanced Cellular Imaging techniques (held first time in September 2014), Receptor Signalling and Trafficking and Molecular Mechanisms of Inflammation.*

On September 4, 2014, the centre organized the annual scientific seminar at St. Olavs Hospital/Faculty of Medicine. The same week we had successful meetings with the Scientific Advisory Board, SAB, and the SAB members were speakers at the seminar, including professors Alan Aderem (Seattle Biomedical Research Institute) Göran Hansson (Karolinska Institute), Stefanie Vogel (University of Maryland) and Douglas Golenbock (University of Massachusetts). The seminar is an important venue for researchers and clinicians working in the field of inflammation research at NTNU and St. Olavs Hospital. The seminar was a great success with more than 150 participants.

The scientific activities at CEMIR have proceeded with very good progress in 2014 and 40 papers have been published, several in high impact journals. Four PhD students completed their theses at the centre. These are some of the scientific highlights in 2014:

– Flo and co-workers published a paper in J. *Immunol.* demonstrating that the antibacterial protein lipocalin 2 is secreted by the urinary tract mucosa in response to uropathogenic E. coli and acts in innate immune defences as a colonization barrier that pathogens must overcome to establish infection.

– Espevik and co-workers published new data in J. *Immunol.* on inflammatory mechanisms underlying inflammatory responses induced by cholesterol crystals. In light of these results, complement inhibition might be an interesting therapeutic approach for treatment of atherosclerosis.

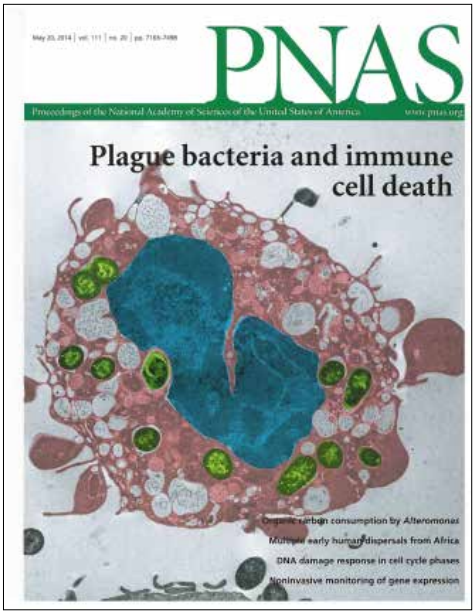
– Latz, Espevik and co-workers reported in *Nature Immunology* that the inflammasome adaptor called ASC recruits and

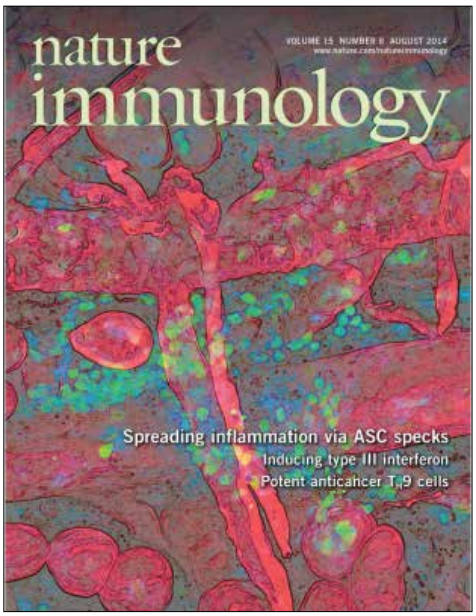
activates caspase-1, which induces maturation of the cytokine interleukin 1 beta and pyroptotic cell death. ASC specks are detected in bodily fluids from inflamed tissues, and autoantibodies to ASC specks develop in patients and mice with autoimmune pathologies. Together these findings reveal extracellular functions of ASC specks and a previously unknown form of cell-to-cell communication. The paper was regarded as ground breaking and its theme was displayed on the front page of Nature Immunology in August 2014.

– The group of Egil Lien published a very important paper in PNAS describing new molecular mechanisms of bacteria-induced cell killing. From the data they propose that caspase-8 and the RIP kinases are key regulators of macrophage cell death, NF-kB and inflammasome activation, and host resistance after infection with the plague bacteria *Yersinia pestis*. The theme of this paper was displayed on the front page of the journal in May 2014.

The Centre of Excellence grant from the Research Council is essential to our existence. CEMIR also receives substantial funding from the Central Norway Regional Health Authority, NTNU, the Norwegian Cancer Society, St.Olavs Hospital and other national and international sources. The long term funding gives us a unique chance to take bolder steps and improves our ability to deliver research that makes lasting impact for the future.

For 2015 I am looking forward to further achievements in inflammation research. We aim at continuing the good scientific progress by recruiting more excellent researchers, facilitating further fruitful cooperation with our national and international collaborators and succeeding with high quality grant applications.



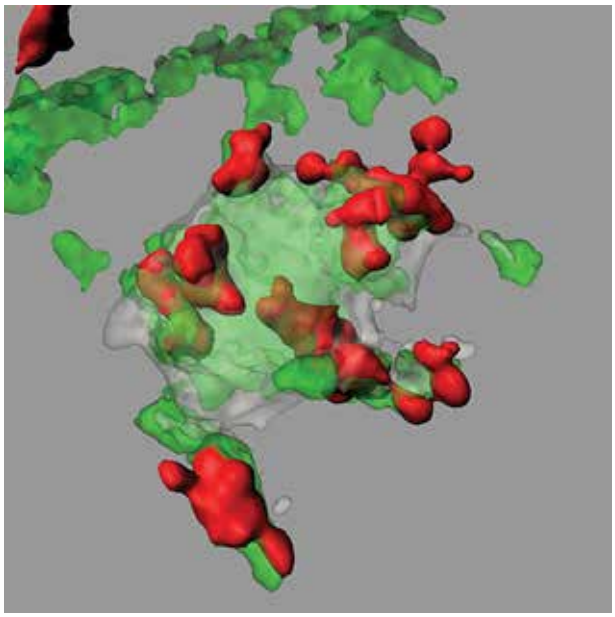


CEMIR RESEARCH ACTIVITY

Theme Manager:
Professor Terje Espevik

Toll-Like Receptor Trafficking

Type I IFNs are classically known as potent antiviral cytokines. More recently the induction of type I IFNs by various types of bacteria in different immune cells has gained increased attention. The impact of type I IFNs on bacterial infections is not clear and spans from immune stimulation to immune suppression which may contribute to the progression of septic shock. 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 in 2014

Lipopolysaccharide (LPS) from Gram-negative bacteria activates TLR4 which needs the adaptor TRAF for inducing IFN-b. In 2014 we have investigated the location and mobility of CD14/LPS, TLR4 and TRAM during TLR4 signalling and how the small GTPase Rab11a regulates TRAM trafficking. We have shown that LPS induces an immobile fraction of TLR4 in punctuates structures in the plasma membrane containing CD14/LPS and clathrin. Rab11a drives TRAM into the endocytic recycling compartment (ERC) and onto endosomes. These data suggest that Rab11a regulates TLR4 mediated IFN-b production through its ability to transport TRAM from Golgi to ERC and further onto endosomes where it interacts with TLR4.

TLR2 is activated by lipoproteins and are thought to mediate signalling through the MyD88 dependent pathway. We have found a new role for TRAM and TRIF also in TLR2 regulation and signaling. The findings broaden our understanding of how Toll/interleukin-1 receptor adaptor proteins may participate in signaling downstream from TLR2.

Moreover, we have delineated the molecular mechanisms on how TLR8 and TLR2 control *Staphylococcus aureus*- induced IFN-b production in human monocytes. CEMIR scientists have also revealed that combined inhibition of CD14 and complement is a promising treatment for both Gram-positive and Gram-negative sepsis.

Major achievements in 2014

- Showed that Rab11a regulates TLR4 mediated IFN-b production through its ability to transport TRAM form Golgi to ERC and further onto endosomes.
- Demonstrated by knock down experiments in primary human macrophages that *Staphylococcus aureus* uses TLR8 for induction of several cytokines.
- Published data suggesting that specific blockade of CD14 and complement factor C5 represents a promising new therapeutic strategy for treatment of polymicrobial sepsis.
- Published data demonstrating that inhibiting complement and CD14 efficiently attenuated *Staphylococcus aureus* – induced inflammation.
- Published results demonstrating a role for TRAM and TRIF in TLR2 signaling.

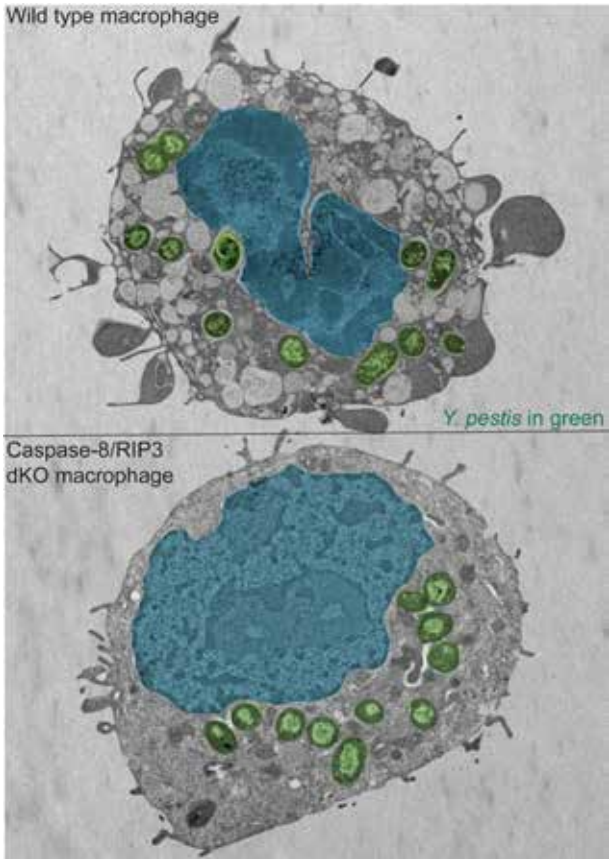
Ambitions for 2015

- To identify the molecular mechanisms behind cross talks between TLR8 and TLR2 in responses induced by different types of Gram-positive bacteria.
- To understand the detailed role of Rab11a and Rab11FIPs in regulating *E.coli*-induced cytokine responses.
- To establish the role of CD150/SLAM in regulating TLR4 and TRAM trafficking and *E.coli*-induced cytokine responses.
- To reveal new components that regulate trafficking of TLR9 from endoplasmic reticulum to the endolysosomes.
- To identify mechanisms behind the improved combined CD14 and complement inhibition of inflammatory responses induced by Gram-positive and Gram-negative bacteria.

The Molecular Basis for Inflammasome Activation

Inflammasomes are multi-molecular complexes that process pro-caspase-1 into the active enzyme. Caspase-1 mediates maturation of pro-forms of cytokines IL-1b 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 Aim 2 is focused on describing mechanisms leading to inflammasome activation, and to study implications on infectious and non-infectious inflammation.

Theme Manager:
Professor Egil Lien



Main activities in 2014

Parts of the work has focused on describing mechanisms for inflammasome activation and cell death induced by Gram-negative bacteria such as *Salmonella*, and *Yersinia*. We have completed a project studying the role of caspase-8 and RIP kinases in host defences towards Yersinia. The main findings were that caspase-8 and RIP1 are critical regulators of caspase-1/inflammasome activation and IL-1b/IL-18 release following infection, in vivo and in vitro, but this pathway also controls cell death and partly NF-kB activation. Mice lacking caspase-8 and RIP3 were very susceptible to bacterial infection, emphasizing the biological significance of the findings.

Work under this theme has also uncovered a novel inflammatory role of extracellular inflammasome complexes containing the adapter molecule ASC. These complexes can be released following cell death and are found in lungs of mice during bacterial pneumonia. The concept of released ASC complexes with inflammatory capacity raises the possibility of systemic effects following localized inflammasome capacity, and suggests a "cytokine-like" role of these complexes. We have evidence for various Type III secretion effector proteins to balance the induction of caspase-1 vs caspase-8 pathways, and this may alter contributions of caspase-1 on cell death. We are also investigating inflammation observed during colitis and obesity, and the roles of NLR proteins and RIP kinases. Other experiments have been focused on mechanisms for vaccine adjuvant action, and the role of Toll-like receptors and inflammasome components in the effects of HIV-1 experimental vaccines. One PhD student has completed studies during 2014.

Major achievements in 2014

- Completed and published a study on the roles of caspase-8 and RIP kinases inflammasome activation, NF-k B activation and cell death in response to bacterial infection.
- Investigated the role of TLRs and inflammasome components on HIV-1 gp120-containing vaccines using different vaccine adjuvants.
- Identified a novel inflammatory role of ASC inflammasome complexes that are released into the extracellular environment, suggesting a systemic signalling role of these complexes
- Found evidence for different bacterial type III secretion system effectors to balance the impact of inflammatory caspases in inflammasome activation

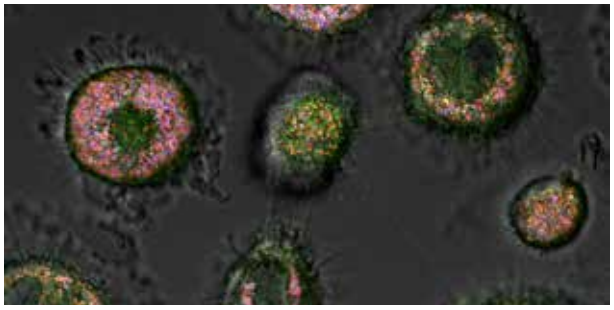
Ambitions for 2015

- Further characterize the role of RIP1 in regulation of inflammasome activation
- Define the role of ASC complexes in immunity
- Identify bacterial type III secretion effectors that balance caspase-1 vs caspase-8 mediated signaling
- Complete studies on sterile inflammation and NLRs in obesity
- Complete studies of inflammasome components and mechanisms of vaccine adjuvant action

Theme Manager:
Professor Jan Kristian Damaas

Inflammatory Responses induced by Cholesterol

Cholesterol crystals (CC) are known to be a hallmark of atherosclerosis with recent studies demonstrating deposition of these crystals in early fatty streak formation as well as penetrating the intima following plaque rupture. Inflammation has also 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 of this theme is to uncover the mechanisms by which CC induce 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 and cytokines.



Main activities in 2014

A continued research focus this year has been on the role of complement activation for CC induced inflammatory responses. Early this year we published a paper showing that CC induce robust complement activation in human serum. We demonstrated also that this response was efficiently attenuated by complement inhibitors. Based on these findings we are now investigating other ways of interfering with CC-induced inflammation. We have recently submitted a paper on how reconstituted high density lipoprotein (HDL) attenuates CC-induced inflammatory responses by binding to CC and subsequently reducing complement activation. Currently, we are exploring how b-cyclodextrin may attenuate CC-induced inflammation. b-cyclodextrin has been shown to remove cholesterol from cultured cells, and we have recently performed several experiments showing that this substance also may alleviate CC-induced inflammation and complement activation.

In parallel to mechanistic studies, we have also investigated the clinical aspects of inflammation in atherosclerosis. First, we have performed genetic studies in the HUNT-database: Among 58,761 participants eligible for inclusion at baseline, we have a total of 1.700 participants diagnosed with incident acute myocardial infarction at hospital during a mean follow-up of 11.3 years. In this cohort, we have investigated specific single nucleotide polymorphisms (SNPs) in a nested-case control study with 3.500 controls. We have also investigated inflammatory biomarkers in the same database. By analyzing serum/plasma samples we have searched for independent predictors for cardiovascular disease. Finally, this year we finished an interventional study. In collaboration with the Departments of Cardiology at St. Olav's Hospital and Oslo University Hospital (OUS) Rikshospitalet we have performed a placebo-controlled, randomized double-blinded study in patients with acute coronary syndrome with toculizumab (blocking monoclonal anti-IL-6R antibody).

Major achievements in 2014

- Demonstrated that cholesterol crystals employ the complement system to induce cytokines and activate the inflammasome/caspase-1 by regulating several cellular responses in human monocytes.
- Showed that endothelial activation by cholesterol crystals is mediated by complement-dependent TNF release, and suggests that complement-inhibition might have a role in alleviating endothelial-induced inflammation in atherosclerosis.
- Submitted a paper showing that reconstituted HDL attenuates CC-induced inflammatory responses
- Showed that the homeostatic chemokines CCL19 and CCL21 are up-regulated in carotid atherosclerosis with the ability of CCL21 to promote lipid accumulation in macrophages and of CCL19 to induce proliferation and matrix metalloproteinases-1 expression in vascular smooth muscle cells could contribute to their pro-atherogenic potential.
- Found an association between prior administrations of the cholesterol lowering drugs statins and a lower total mortality in Gram-negative bloodstream infections, suggesting that statins exerts their anti-inflammatory and pleiotropic effects mainly through TLR4-inhibition.
- Finished the double blinded placebo controlled study: "Effect of the interleukin-6 receptor antagonist Tocilizumab in non-ST elevation myocardial infarction". Abstract has been submitted for presentation at international conferences and the first manuscript is under preparation.

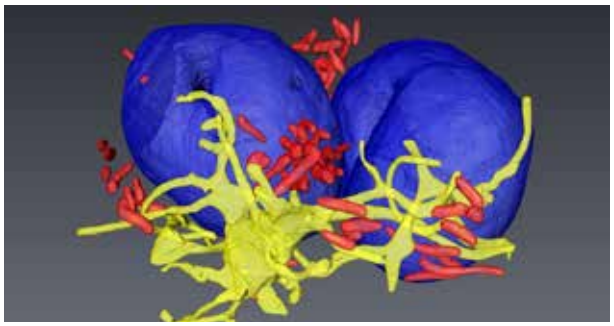
Ambitions for 2015

- To test the effect of cholesterol crystal dissolution by b-cyclodextrin in human cells and in mouse models of atherosclerosis.
- To establish the role of the coagulation system in cholesterol crystal-induced inflammation.
- To perform sub-studies on the material from the clinical study on patients with acute coronary syndrome with toculizumab, particularly profiling of the cytokine network and analyses of complement components (including gene expression studies in peripheral blood).
- Start a clinical multicenter study with toculizumab in patients with transmural ST-elevation infarction.
- Analyze new inflammatory biomarkers in the HUNT-database.

Theme Manager:
Professor Trude Helen Flo

Inflammation & Autophagy

Cells frequently experience stress with increased levels of reactive oxygen species (ROS). ROS may contribute 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. In theme 4 we aim to define novel relations between oxidative stress, signaling through PRRs and autophagy in inflammatory diseases, including mycobacterial infections where the focus is molecular host defense mechanisms involved in immunity to mycobacterial pathogens and virulence strategies employed by mycobacteria to parasitize host cells.



Main activities in 2014

This year we established the role of a key oxidative stress protein in regulation of inflammation and survival of pathogenic mycobacteria in primary human macrophages. The work is continuing in 2015 to reveal how inflammatory signaling is related to mycobacterial trafficking within macrophages, and to detail signaling pathways initiated. We have worked with mycobacterial virulence factors, including iron acquisition systems and mycobacterial proteins possibly interfering with host defense pathways. In 2014 we also pioneered the use of Focused Ion-Beam Scanning Electron Microscopy (FIB-SEM) together with light microscopy for correlative imaging of mycobacterium-infected macrophages in nanoscale 3D. During 2014 we have also focused on how omega-3 fatty acids mobilize the cellular oxidative stress defense and protein quality control and may reduce the risk of neurodegenerative diseases. We are now extending on these findings to determine if the same mechanisms also contribute to anti-inflammatory effects of marine lipids and how this might be influenced by external antioxidants. Moreover, we have studied how tumor derived pro-inflammatory cytokines can induce weight loss in cancer patients and find indications for a systematically induced autophagy. To better understand how oxidative stress defense and autophagy could be deregulated in disease we have established full genome and transcriptome sequencing of a breast cancer metastasis model to identify mutations and expression disturbances that results in elevated oxidative stress defense and increased autophagy in aggressive cancers.

In 2014 we recruited two post docs, one PhD student, two medical research students and seven master students that are currently working on theme 4 projects. In addition we have a guest researcher visiting.

Major achievements in 2014

- Established the role of lipocalin 2 in urinary tract infection
- Established the role of a key oxidative stress protein in regulation of inflammation and survival of *M. avium* in primary human macrophages
- Established that a novel antimycobacterial compound acts as an iron chelator
- Pioneered the use of Focused Ion-Beam Scanning Electron Microscopy together with light microscopy for correlative imaging of mycobacterium-infected macrophages in nanoscale 3D
- Established exome and transcriptome sequencing in a model of cancer metastasis
- Established NanoString® analyses of effects on marine lipids on macrophage activation

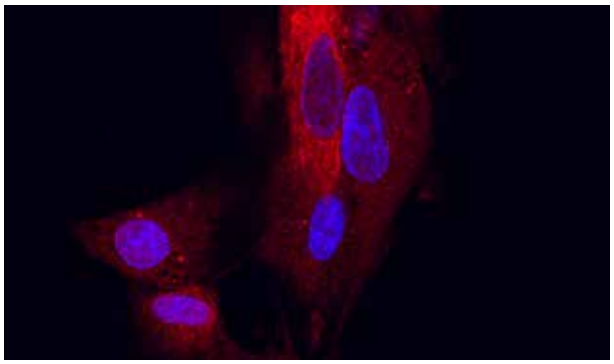
Ambitions for 2015

- Elucidate on HIV proteins interfering with autophagy in T-cells
- Clinical relevance of the oxidative stress protein in sepsis patients (GWAS study)
- Further improve correlative imaging using light microscopy and FIB-SEM
- Elucidate on compartmentalized signaling in mycobacterium-infected macrophages
- Elucidate on the role of lipid metabolism in HIV disease susceptibility and progression
- Sequencing of *M. avium* transposon mutant library: identify mutants in iron metabolism and intramacrophage virulence genes
- Establish routines and training to work with *M. tuberculosis* in the new BSL3 lab to be opened in 2015 in Kunnskapssenteret.
- Define how pro-inflammatory cytokines induce autophagy
- Determine if TGF-b family members controls autophagy indirectly via induced secretion of pro-inflammatory cytokines
- Determine how the secretion of discrete pro-inflammatory cytokines from activated macrophages are affected by omega-3 polyunsaturated fatty acids
- Investigate the cause and consequence of activated oxidative stress defense in aggressive cancer development
- Identify changes in the exome and transcriptome that encode adaptations starvation and metastatic growth in cancer cells

Theme Manager:
Associate Professor
Ann-Charlotte Iversen

Inflammation underlying Atherosclerosis and Preeclampsia

Cardiovascular disease (CVD) is a major cause of human illness and death worldwide where inflammation plays a key role. Women with preeclampsia (PE) have increased risk for later CVD and develop atherosclerosis-like lesions in uterine wall arteries during pregnancy, suggesting shared underlying mechanisms for disease. Inflammatory mediators like oxidized lipoproteins and cholesterol crystals are implicated, but with unknown molecular action. We hypothesize that pattern recognition receptor (PRR) mediated inflammation is central for the preeclampsia pathogenesis and the gender-specificity of CVD. In this theme we aim to investigate how PRR-initiated inflammatory processes of preeclampsia in pregnancy are related to later development of CVD.



Main activities in 2014

The work on inflammation in preeclampsia in relation to CVD has in 2014 been focused on completion and diagnostic characterization of two pregnancy-related biobanks that is extensively used for studies of specific PRR involvement in the harmful inflammation of preeclampsia, and metabolomic profiling of the disease. The predictive value of metabolomic profiling and cytokine response for preeclampsia is investigated in early pregnancies from the ScreenTox Study, and combined heritability of preeclampsia and CVD traits and shared risk genes are being studied based on the HUNT Study and the Preeclampsia Family Biobank. Overall, this work has added new knowledge to the phenotypic relation between development of preeclampsia and CVD, and led to discovery of novel predictive preeclampsia biomarkers and the importance for trophoblast PRR mediated inflammation in preeclampsia development.

Major achievements in 2014

- Discovered broad PRR mediated inflammation by primary trophoblasts, defining an inflammatory role for trophoblasts in placental development in normal pregnancy and in development of preeclampsia.
- NMR profiling of maternal serum and urine has been established for detailed profiling of preeclampsia specific metabolic changes, with lipid profiles similar to in CVD.
- Discovered novel predictive metabolomic biomarkers for preeclampsia.
- Revealed that preeclampsia risk genes are associated with cardiovascular risk traits in preeclamptic mothers and children born from preeclamptic pregnancies, and that preeclampsia and chronic hypertension show shared heritability in families with increased occurrence of preeclampsia.

Ambitions for 2015

- Continued collection of pregnancy-related biobanks and establishment of a biobank collection of adipose tissue for inflammation studies.
- Elucidate specific PRR mechanisms initiating the harmful inflammation of preeclampsia, focusing on atherotic lesions in uterine wall arteries and placental trophoblasts.
- Improve prediction models and subgrouping of preeclampsia, and find new etiologic clues to the disease by inflammatory and metabolomic profiling.
- Identification of gene variants of relevance to the pathogenesis of preeclampsia and cardiovascular diseases, and perform functional risk gene analysis in placental tissue.

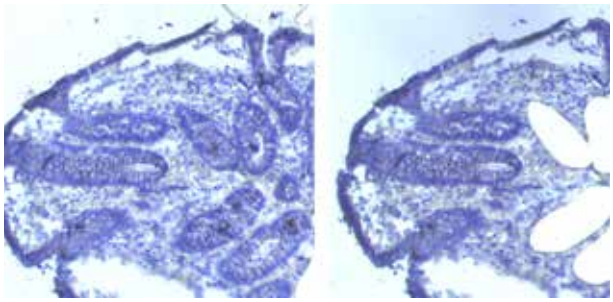
Theme Manager:
Professor Arne Kristian Sandvik

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a major clinical problem, with approximately 2 mill Europeans chronically affected by either ulcerative colitis or Crohn's disease. Current hypotheses on etiology and pathogenesis include dysfunctional inflammatory pathways including PRRs and autophagy, with approximately 100 mutations 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 IBD disease and subsequently restored in remission.

Main activities in 2014

The theme work has proceeded to unravel the role of REG4, a C-type lectin, in IBD. Another main activity is studies on antimicrobial peptides in IBD, in particular lipocalin 2. In 2014 a Health Authority grant was activated with one PhD student having the interaction between the neuroendocrine and immune system as his main project. An already large biobank with patient material and clinical information is continuously expanding, and the use of material refined with methods such as e.g. microdissection of biopsies and cell-specific gene expression studies.



Major achievements in 2014

- Discovered a cell line that expresses REG4 and enables detailed studies of its regulation, and established methods to identify a putative REG4 target/receptor.
- Localized lipocalin 2 to specific cell types in the intestine, and started studies on its regulation and performance as a disease marker in IBD.
- Established laser capture microscopy combined with high-quality RNASeq on clinical biopsies from IBD patients.

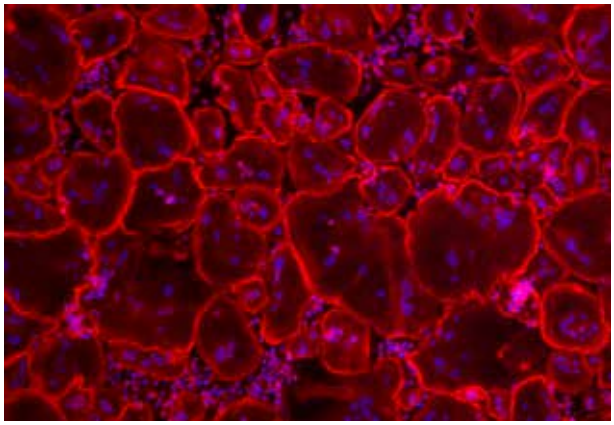
Ambitions for 2015

- Clarify the detailed (possibly innate) regulation of REG4, and identify its target/receptor.
- Conclude as to the performance of lipocalin 2 as a clinically usable biomarker for inflammation in IBD.
- Clarify the regulation of 5-HT synthesis, release and extracellular availability in the mucosa in IBD and its role in relation to inflammatory fibrosis.
- Generate novel hypotheses on epithelial function (integrity and defense) in IBD, using high-quality tissue sub-specific RNASeq.

Theme Manager:
Professor Therese Standal

Inflammation underlying Bone Destruction

Bone remodeling is the reconstruction of the skeleton by osteoclastic bone resorption followed by osteoblastic bone formation. Remodeling is a tightly regulated process, which, however, in some pathological conditions gets out of control. Destruction of bone is common in cancers like multiple myeloma and breast- and prostate cancer metastasizing to bone, in inflammatory diseases such as inflammatory bowel disorder and autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus. The main aim of this theme is to reveal underlying mechanisms for bone loss associated with cancer and inflammation.



Main activities in 2014

In 2014 we worked mainly on how inflammatory signals regulate the expression and function of receptor activator of nuclear factor kappa-B ligand (RANKL), the main osteoclast activator, on osteoblasts. In particular, we have focused on addressing whether RANKL is found on exosomes, which signals that may trigger exosomal RANKL expression, and whether this form of RANKL has a different biological effect compared with cell surface RANKL. Further, we studied how TLR-TRIF- signaling induced expression of cytokines in human mesenchymal stem cells. We have also identified IL32 as a novel cytokine produced by malignant plasma cells during hypoxia, and we are currently addressing the role of IL32 in myeloma pathogenesis. Another important activity has been the establishment of a mouse model for myeloma, and in 2014 we initiated the first pre-clinical drug testing in this human-mouse hybrid model here in Trondheim. Two PhD students completed their degrees in 2014, and one post doc was recruited.

Major achievements in 2014

- Demonstrated that RANKL is present on exosomes
- Established a humanized mouse model for mulitple myeloma in Trondheim

Ambitions for 2015

- To continue our studies on the effect of inflammatory signals on mesenchymal stem cell function.
- To identify and characterize endogenous PRR ligands in bone marrow samples obtained from myeloma patients.
- To examine the role of IL32 in multiple myeloma.
- To establish the role of exosomal RANKL for bone remodeling *in vivo*.

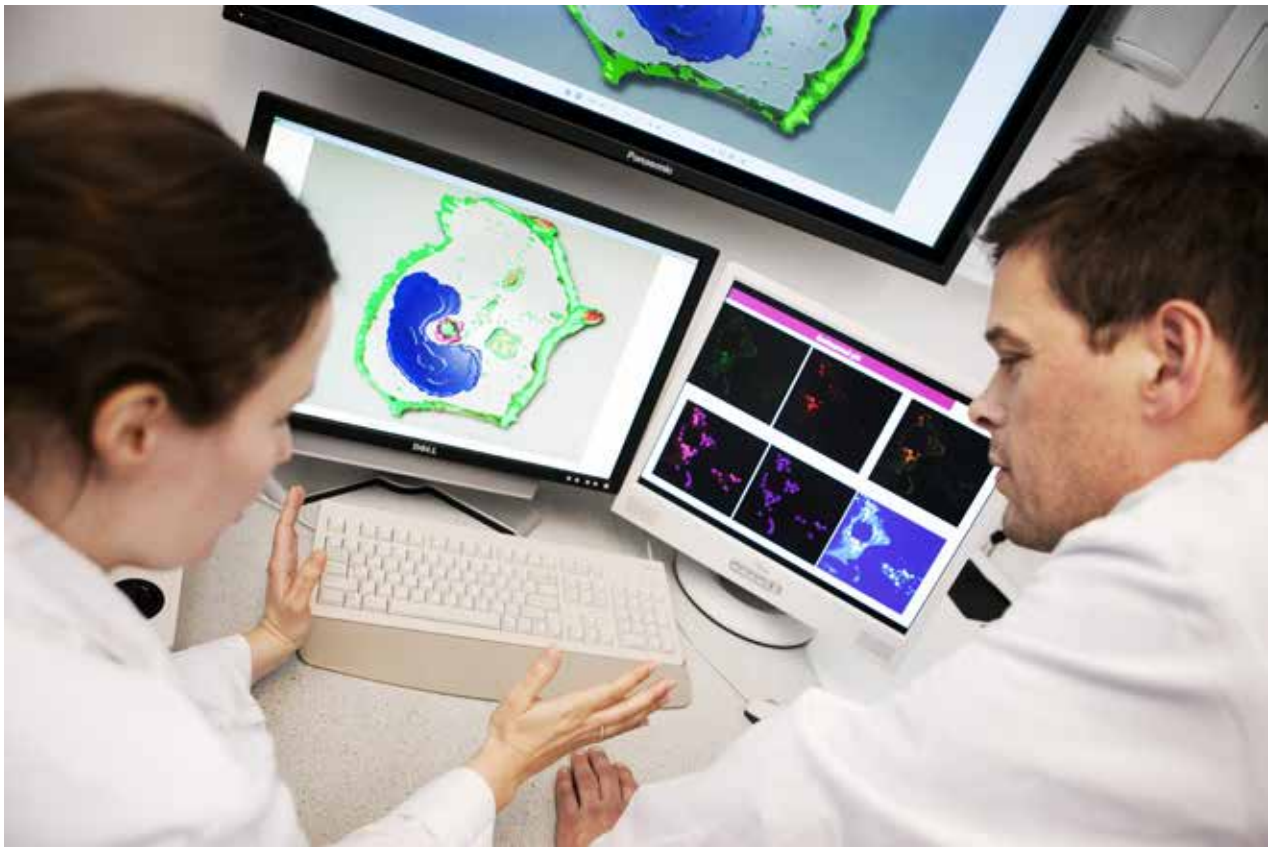
CEMIR RESEARCH GROUPS

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 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. Moreover, we work on the inflammatory responses induced by cholesterol crystals. The aim of this subproject is to identify and characterize molecular mechanisms of inflammatory responses that can be targeted for the design of 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 STED super-resolution laser confocal microscope and a TIRF microscope that have been installed in the new CEMIR laboratories. The inflammation Research Group is contributing to several of the basic research oriented CEMIR themes (themes 1-4) as well as having cooperations with the more clinical orientated research themes (Sandvik and Damås).

The research group is led by Professor Terje Espevik and currently consists of 23 persons including 6 PhD students, 7 post docs, 6 research scientists and 4 staff engineers. The group has close collaborations with the CEMIR affiliated professors, Mollnes, Lien, Fitzgerald, Stenmark and Latz. Moreover, the group is also actively involved in collaborative projects at national (Aukrust and Yndestad, University of Oslo) and international levels (G. Teti, University of Messina, Italy, and M. McCaffrey, University of Cork, UK).



The Research Group on Molecular Mechanisms of Mycobacterial Infections

Tuberculosis (TB) kills more than 1.5 million people worldwide each year, and an estimated 2 billion individuals carry latent *Mycobacterium tuberculosis* (Mtb) infection. 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. The inter-connected roles of trafficking and compartmentalized PRR signaling, iron metabolism and autophagy for mycobacterial survival make these processes 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. T cell effector functions in patients co-infected with mycobacteria and HIV are impaired and we currently study the impact of concomitant HIV-infection on anti-mycobacterial host defenses, including lipid metabolism and autophagy in T-cells. We believe our basic research strategy may contribute to revealing new therapeutic targets and vaccine development.

The Research Group is led by professor Trude H. Flo and includes two more research scientists, four post docs, four PhD students, one staff engineer, two medical research students and master students. We have developed expertise, methods and tools to study mycobacteria and the host innate and adaptive immune defenses both in vitro 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 new BSL3 facility at Kunnskapssenteret for live imaging of Mtb infections. Transposon mutant libraries with more than 150 000 mutants in *M. smegmatis, M. avium* and Mtb are available. We are mainly focused on CEMIR theme 4 but collaborate closely with the autophagy group (G Bjørkøy), the inflammation group (T Espevik, JK Damås) and with CEMIR affiliated professor D Underhill. Together with Ø Halaas (NTNU, nanomedicine) we also pioneer the use of Focused Ion-Beam Scanning Electron Microscopy (FIB-SEM) at NTNU Nanolab to establish nanoscale high resolution imaging of intracellular mycobacterial infections using. Central external collaborators are T Johansen (UiT, autophagy), A Brech (UiO, EM), E Rubin (Harvard School of Public Health, mycobacteria), TR Hawn (U Washington, infections), and A Aderem (Seattle Biomed).

The Autophagy and Oxidative Stress Defense Group

The autophagy group focuses on the role of this intracellular degradation route in the prevention of age-related diseases and how this mechanism protects against cellular oxidative stress. In preventive settings we are studying cellular responses towards n-3 polyunsaturated fatty acids (PUFAs) in normal, non-transformed cell models and in primary cells isolated from healthy donors. The responses studied include changes in autophagy and the oxidative stress defense system coordinated by Nrf2. We also study if these responses are involved in the anti-inflammatory roles of n-3 PUFAs and if these lipids can affect the development of proteinopathies. For the disease promoting functions of autophagy and oxidative stress responses, we particularly study the formation of aggressive tumors and try to decipher how these cytoprotective processes are turned into mechanisms that support growth and survival of cancer cells under stressful conditions. Finally, the group investigates the putative role of systemically activated autophagy in patients that develops cancer cachexia. Particularly, the role of tumor derived pro-inflammatory signaling substances in the activation of lysosomal protein degradation in muscle cells and tissues are investigated.

The group is led by Professor Geir Bjørkøy and consists of one and a half senior technicians, four PhD students and two master students. The group has established several cellular models of both normal and cancerous cells to study regulation of autophagy by both protein analyses, imaging approaches and flow cytometry. In addition, the group recently established genome and transcriptome sequencing of cancer models to try to decode how autophagy and oxidative stress defense may be deregulated in aggressive cancers. The group is also involved in determining bioactivity for novel targeted kinase inhibitors designed and synthesized by a collaborating group at NTNU and HiST (B. Hoff and E. Sundby). A close collaboration with the K.G.Jebsen centre on Myelomatosis Research headed by A. Sundan at NTNU allows studies of the role of oxidative stress responses and autophagy in patients treated with proteasomal inhibitors. External collaborators include the groups of T. Johansen (UiT), P.E. Lønning (UiB), K. Fearon (Univ of Edinburgh) and M. Komatsu (Tokyo Metropolitan Univ.).

The Research Group on Inflammation and Genetics in Pregnancy

The Research Group of Inflammation and Genetics in Pregnancy works closely with several other researchers at CEMIR and the core facility CMIC, and is particularly linked to themes focusing on the molecular studies of lipids and cholesterol crystals and activation of inflammasomes, TLR2 and TLR4 (Professors Espevik and Damås). Several pregnancy-based biobanks are collected and administered by the research group and provide unique materials for the molecular inflammation analyses.

The broad research approach involving biobanking, molecular studies, genetics and metabolomics, is made possible by a strong collaboration between clinical departments and basic researchers in different disciplines both nationally and internationally. Central collaborators include Professor Line Bjørge at Haukeland University Hospital, The Women's Clinic at St Olavs Hospital, Professor Kjell Salvesen at the Central Norway Regional Health Authority and Professors Tone Bathen and Torstein Vik at NTNU. Professor Catherine Hedrick at La Jolla Institute for Allergy and Immunology in San Diego has hosted Ann-Charlotte Iversen as Visiting Scientist in 2014-2015 for study of mice models of atherosclerosis and pregnancy complications. The Research Group is partner in a large 12-partner EU 7FP project InterPregGen coordinated by Professor Linda Morgan at University of Nottingham, aiming to unravel genetic risk factors for preeclampsia in relation to cardiovascular risk traits, based on the world's largest pregnancy based cohort collaboration for genetic studies, and the research group at CEMIR is involved with a pregnancy cohort from the HUNT Study and are responsible for functional placental risk gene analysis.

In preeclampsia extensive atherotic lesions develop in the uterine wall arteries and these closely resemble atherosclerotic lesions, but a causative role in preeclampsia has not been investigated. The Research Group hold a unique collection of decidual tissues containing atherotic lesions and focus on revealing the inflammatory processes in atherosis and how this influence initial placental development and eventually preeclampsia. Lessons are learned from the central role of cholesterol crystals and PRR activation in atherosclerosis development and CVD. In addition the central role of the fetal throphoblasts in the harmful placental inflammation in preeclampsia is focus for molecular inflammation studies.

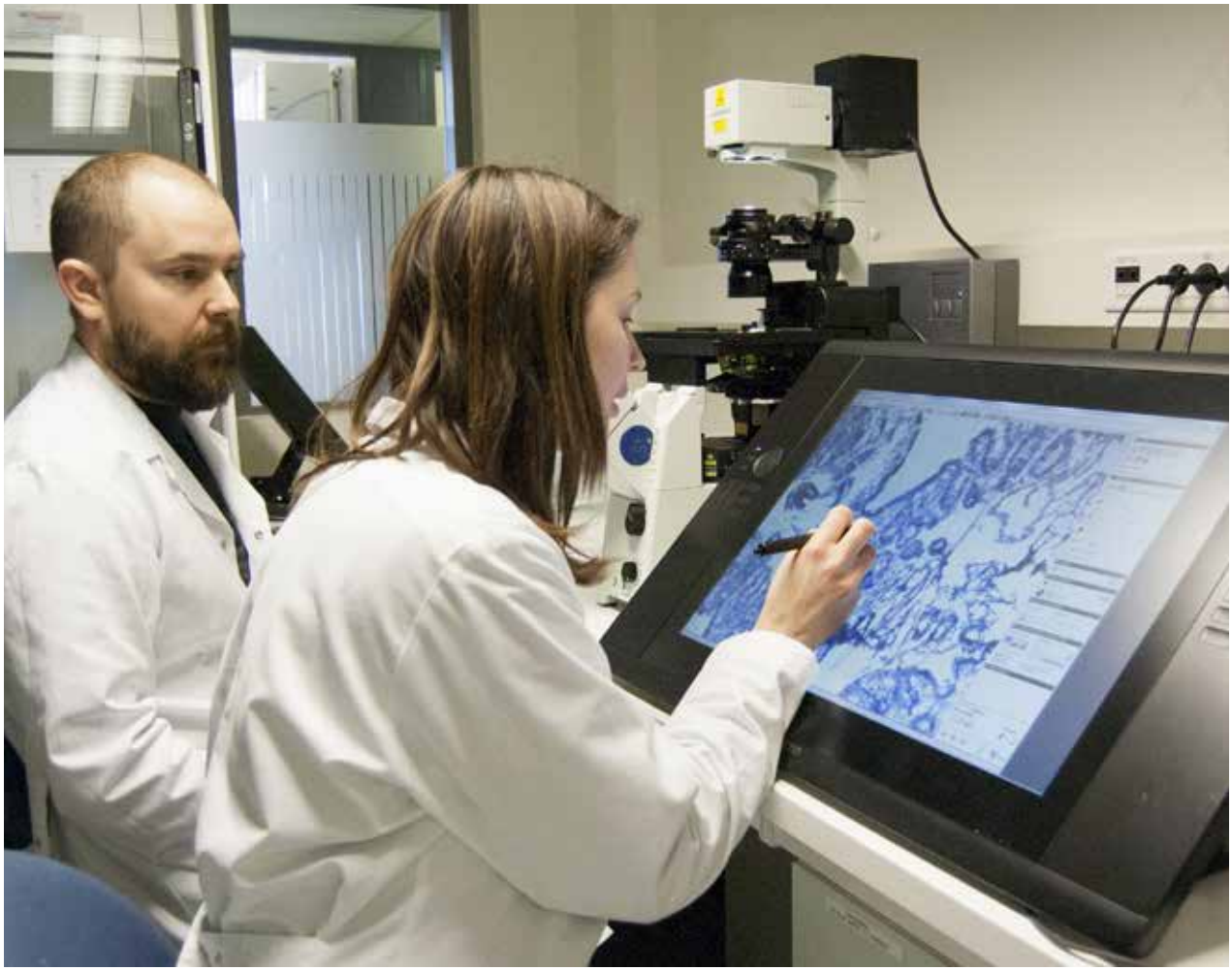
The Research Group is led by Associate Professor Ann-Charlotte Iversen. In 2014 the group counted 10 persons; Professor Rigmor Austgulen, 1 post doc, 6 PhD students and 1 staff engineer. One PhD MD student defended her thesis and one new PhD MD joined the group in 2014 after completing her master in the group.

The Inflammatory Bowel Diseases Research Group

The inflammatory bowel diseases (IBD) research group was established to study pathogenetic mechanisms in IBD, and use this knowledge to contribute to improved diagnostics and prognostics. Another central aim is to discover novel therapeutic targets. In general, the IBD research projects aim at understanding central mechanisms for mucosal homeostasis and how these are disrupted in active disease and subsequently restored in remission. Example projects are the effect of hypoxia on the epithelium, the role of guanylin/uroguanylin in inflammation, the action and regulation of mucosal antimicrobial peptides and how the diffuse neuroendocrine system interacts with immune signaling in IBD. The CEMIR related projects are done in close collaboration with the CEMIR groups working with innate immune mechanisms (Professors T. Espevik and J.K. Damås).

The IBD group is closely connected with clinical medicine. The two group managers, Arne Sandvik and Bjørn Gustafsson, professors at NTNU and clinical gastroenterologists. The group collaborates with clinicians in 7 different hospitals in the Central Norway Health Region, and regional hospital staff will be involved in translational research projects. One of the two IBD group leaders also administers the faculty Genomics Core Facility (microarray and sequencing), and is experienced within transcriptome analysis and bioinformatics. The group has access to excellent animal experimental facilities, and is among few in the world doing routine colonoscopy on rat and mouse IBD models.

The IBD research group is led by two Professors (in gastroenterology) with side affiliations as senior consultants in clinical medicine. Other staff in the group is one senior researcher and one associate Professor working partly within IBD. The group includes one adjunct Professor from Yale University. A significant change in staff has taken place during 2014 in that one former PhD student after her dissertation has joined the group in a 50/50 position as researcher/consultant physician. Moreover, three new PhD students have joined the group during the autumn of 2014 together with a senior laboratory technician.



The Bone Disease Research Group

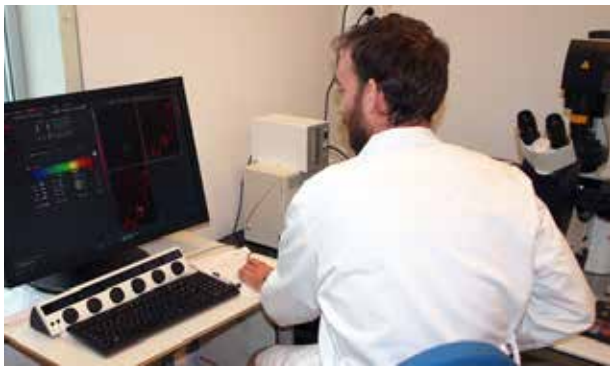
The bone disease group is a small group consisting of one senior research scientist, two post doctors and one PhD student. The group manager is Professor Therese Standal. The PhD student will submit her thesis in April 2015.

The research is focused on how cancer and inflammation influence bone, and we are in particular interested in understating the molecular mechanisms for the bone destruction associated with multiple myeloma and rheumatoid arthritis. The group is affiliated with the K.G. Jebsen center for myeloma research and profit from a close collaboration with clinicians and researchers at this center. Further, in close collaboration with the Department of Rheumatology at St.Olavs Hospital a biobank for arthritis was established in 2009. Hence, we have access to well characterized samples from both myeloma patients and patients with different subtypes of arthritis. We also have established a mouse model for multiple myeloma, which has given us new opportunities in terms of in vivo experiments.

NEW LABORATORIES IN 2014

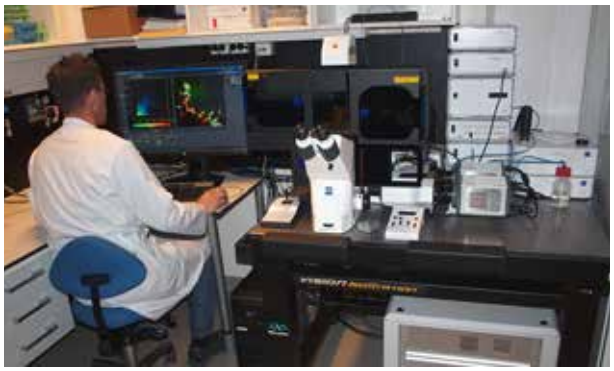
Our new laboratories in the knowledge centre opened in June 2014. New advanced instruments have been installed and our laboratories contain state of the art cellular imaging instruments:

- a 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 (BSL) 3 facility

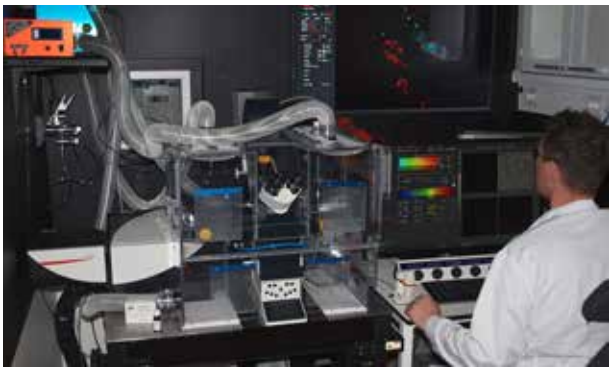


Leica SP8 confocal on BSL3 lab

BD-FACS Aria cell sorter



Leica SP8 STED-3X super resolution microscope

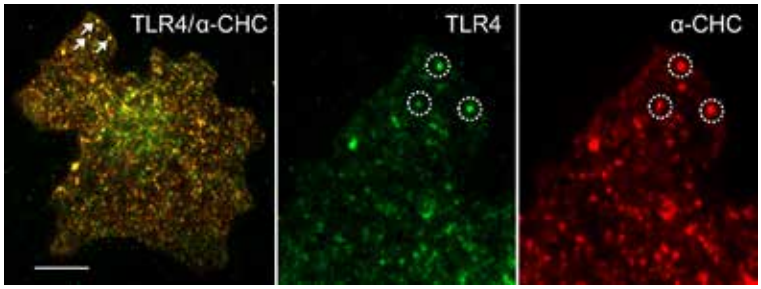


Zeiss TIRF microscope

General laboratory

CEMIR-USE OF THE IMAGING CORE FACILITY

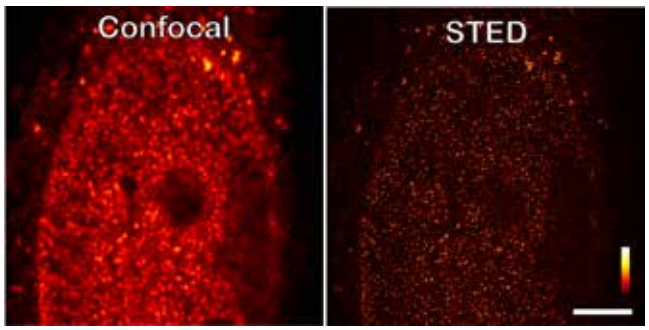
Researchers and students at CEMIR have access to a multitude of different imaging techniques, for live cell studies as well as imaging of fixed cells and tissue preparations. These instruments are all part of the recently established Cellular and Molecular Imaging Core Facility (CMIC) at Faculty of Medicine, NTNU. https://www.ntnu.edu/dmf/cmic. In 2014 a super resolution light microscope and a total internal reflection fluorescence microscope were installed at CMIC and placed in the CEMIR laboratories.



Leica SP8 STED 3X

STED is the abbreviation of STimulated Emission Depletion and is a technique applied to microscopy, providing better resolution than traditional confocal microscopy. The STED resolution improvements come from a reduction of the physical dimensions in the focal spot from where the fluorescence can be emitted. This is achieved by introducing a depletion donut mask overlapping the diffraction-limited spot in the focus plane. By increasing the laser power of the depletion laser the donut gets bigger and consequently the spot gets smaller. This is achieved in all three dimensions.

The new Leica SP8 STED 3X microscope is equipped with a pulsed white-light laser that works in conjunction with an AOBS (acoustic optical beam splitter) providing any wavelengths between 470 and 670nm. The STED is provided by 3 powerful depletion lasers with wavelength 592, 660 and 775nm covering fluorophores of most of the visual spectra. It is fitted with sensitive hybrid detectors (HyDs) with time gating of the fluorescence signals and a 3D vortex for adjusting the ratio between the lateral and axial resolution. The microscope also has a high speed resonant scanner, a fast piezo z-drive and an incubator for live cell imaging.



Zeiss TIRF 3

Total Internal Reflection Fluorescence (TIRF) microscopy is the ideal tool to study cellular processes in the plasma membrane area. Because only a thin layer of the cell above the cover glass is illuminated, the rest of the cell is not disturbed. This fact results in a good signal to noise level, low bleaching, less stress to the cell and enables long time live imaging.

The new Zeiss TIRF 3 is a laser-based microscope that also works in epi-fluorescence mode. The system has 4 high-powered lasers for rapid live cell photo bleaching experiments and two sensitive EMCCD cameras with a chromatic splitter for acquiring two fluorescent probes simultaneously. This microscope is equipped with excellent optics for enhanced resolution in TIRF mode and is also fitted with an incubator.

COOPERATION WITH CLINICAL DEPARTMENTS

Chronic inflammatory processes play an important role in the pathophysiological process in diseases such as atherosclerosis, diabetes, rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and various neurological disorders. During the last years several inflammatory mediators have been identified as novel treatment targets in disorders such as in RA and IBD, and medications blocking or modulating these targets have been very successful. The vision of CEMIR is to lay the foundation for identifying new therapeutic targets and in developing new diagnostic tools for inflammatory diseases through research in molecular innate immune responses.

A close collaboration with the clinical departments is crucial for addressing our goal. 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 in the clinic 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 patients with diseases such as coronary artery disease (CAD), IBD and multiple myeloma. Samples from these biobanks were included in several papers in 2014, often demonstrating the human and in vivo relevance of data from experimental models. Many of these patients have also previously been included in the HUNT cohort with available genomic DNA and serum/plasma. In 2014 we have performed several studies investigating genetic polymorphisms and plasma levels of cytokines as biomarkers for disease, hoping to identify novel diagnostic and prognostic tools for chronic inflammatory disorders such as CAD and IBD.

In 2014 we have also finished a placebo-controlled, randomized double-blinded study in patients with acute coronary syndrome. In this study we explored the effect of toculizumab, a blocking monoclonal anti-IL-6 receptor antibody, on inflammatory processes related to atherosclerosis and myocardial damage. This study was performed in collaboration with the Institute for Internal Medicine, University in Oslo and the Departments of Cardiology at St. Olav's Hospital and Oslo University Hospital (OUS) Rikshospitalet. This study is the first to demonstrate that IL-6 inhibition is safe and beneficial in CAD patients, and accordingly this new treatment principle will be patented by CEMIR and our collaborating partners. As important, this study shows that the interaction between CEMIR and the clinical departments is close, and that the ability of performing such proof-of-concept studies by blocking inflammatory mediators or signaling pathways in a clinical setting, is one of the strengths of CEMIR.

St.Olavs hospital/Faculty of Medicine in the lower right corner .

INTERNATIONAL COOPERATION

CEMIR has a comprehensive international network, and it's our goal to further develop long-term international cooperation with excellent scientists and institutions.

In 2013 CEMIR recruited six outstanding researchers as adjunct professors, 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 (held first time in September 2014), Receptor Signalling and Trafficking and Molecular Mechanisms of Inflammation (both started in 2013).

Moreover the adjunct Professors contribute with presentations at our annual seminar on inflammation at NTNU/ St.Olavs Hospital. They are also tightly involved with CEMIR by co-supervising our PhD and postdoctoral candidates. Staff members are offered the possibility to spend extended periods in their laboratories.

In 2014 five CEMIR PhDs and Post doctors were visiting researchers in the labs of the adjunct Professors (at University of Massachusetts, Cedars-Sinai Medical Center and University of Bonn). We consider this an important component of the researcher training, networking and internationalization of our research.

CEMIR has an international work environment - in 2014, 20 nationalities were represented in our staff. We also hosted a visiting researcher from Italy; A PhD candidate from the lab of Professor Giuseppe Teti, university of Messina, stayed with CEMIR for 12 month, connected to Terje Espevik's research group.

Other central international collaborators in 2014:

- Aderem, Alan, Seattle Biomed, USA
- Benedict, Chris, La Jolla Institute, USA
- DeWan, Andrew T., Yale School of Public Health, USA
- European Myeloma Network
- Fearon, Ken , Univ. of Edinburgh, UK
- Goguen, Jon, Univ. of Massachusets, USA
- Hawn, Thomas R., University of Washington, USA
- Ingalls, Robin, Boston University, USA
- Kidd, Kenneth, Yale, USA
- Komatsu, Masaaki, Tokyo Metropolitan Univ., Japan
- McCaffrey, Mary, Univ. of Cork, UK
- Mecsas, Joan, Tokyo Univ. of Foreign Studies, Japan
- Mobley, Harry LT, Univ. Of Michigan Medical School, USA
- Moses, Eric, Univ. of Western Australia
- O`Neill, Luke, Trinity, Univ. of Oslo
- Rubin, Eric, Harvard School of Public Health, USA
- Teti, Giuseppe, Univ. of Messina, Italy

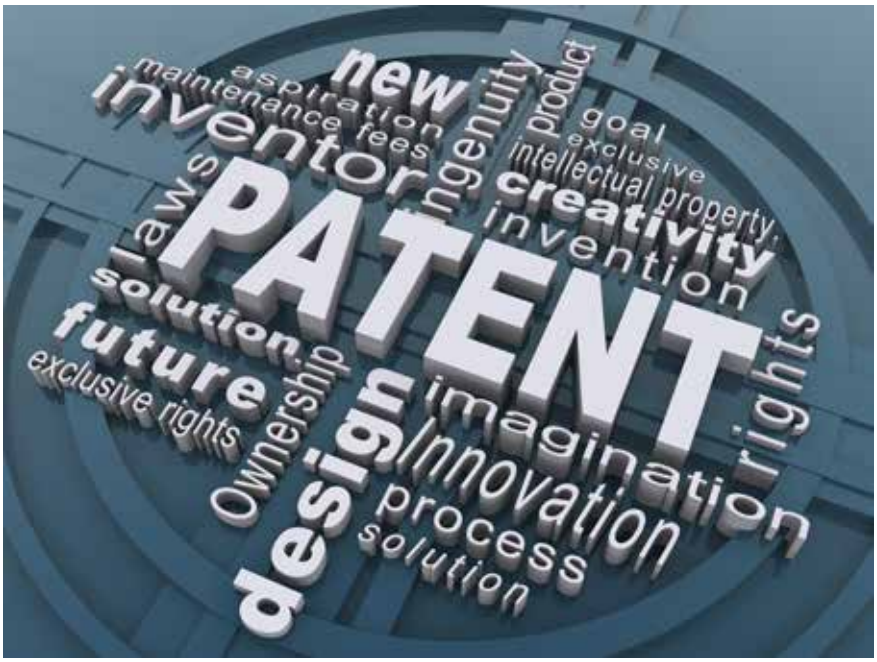
INNOVATION AND PATENTS

The concept of double-blockade of complement and CD14 to attenuate inflammation

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. Using specific complement inhibitors of the central components C3 and C5 we observed that certain branches of inflammation was substantially inhibited, including granulocyte activation with surface receptor up-regulation and oxidative burst, whereas other mediators including a number of cytokines were less complement dependent. CD14 is a co-receptor for several of the Toll-like receptor molecules, in particular TLR4 and TLR2 and thus could be another key target for inhibition. Using specific antibodies to block CD14 we documented a marked reduction in a broad panel of cytokines and monocyte-mediated responses, differential from the complement-dependent responses.

Based on these observations we combined complement inhibitors (C3 or C5) with anti-CD14 and found these to be crucial "bottle-neck" molecules which virtually abolished the whole inflammatory response when inhibited in combination. This was shown for both exogenous danger signals like Gram-negative and Gram-positive bacteria in vitro (human) and in vivo (pigs and baboons), for polymicrobial sepsis in mice and pigs, and for endogenous danger like meconium, which is sterile and induces a serious inflammation in newborns. In a whole genome array we documented that 70% of all Gram-negative bacterial induced genes (a total of >2000) were reversed by an average of >80% signal by combined inhibition of C3 and CD14. Thus, blocking of two "bottle-neck" molecules (C3 or C5 of complement) and CD14, at the very first step of danger recognition might be a potent therapeutic strategy to attenuate undesired inflammation occurring in a number of pathophysiological states leading to different disease conditions.

The principle of double-blockage of complement and CD14 to attenuate inflammation 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 under production as a recombinant humanized antibody for therapeutic use Three patents have been posted related to this scientific project. A formal collaboration contract has been made with a company producing a C5 inhibitor under clinical phase I studies. The vision 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.



COMPLETED PhDs IN 2014

Ann Elisabeth Østvik defended her thesis «Innate immune responses in colonic mucosa during inflammatory bowel disease – effects of TLR3 signaling» on April 24, 2014 at NTNU, Center of Molecular Inflammation Research (CEMIR). The experimental work was conducted at the Department of Cancer Research and Molecular Medicine at NTNU and St.Olavs hospital with Professor Arne Kristian Sandvik as supervisor and Professors Terje Espevik and Helge Waldum as co-supervisors.

Mari Løset defended her thesis « Genetic Predisposition to Preeclampsia - Genetic Association Studies on Population-Based Cohorts and Transcriptional Studies on Decidua Basalis Tissue» on February 7, 2014 at NTNU, Center of Molecular Inflammation Research (CEMIR). The experimental work was conducted at the Department of Cancer Research and Molecular Medicine at NTNU with Professor Rigmor Austgulen and senior research scientist Ann-Charlotte Iversen as supervisors and Professor Eric Moses and post doctor Linda Tømmerdalen Roten as co-supervisors.

Siv Helen Moen defended her thesis « Influence of inflammation and cancer on mesenchymal stem cell function» on January 29, 2014 at NTNU, Center of Molecular Inflammation Research (CEMIR) and KG Jebsen Center for Myeloma Research. The experimental work was conducted at the Department of Cancer Research and Molecular Medicine at NTNU with senior research scientist Therese Standal as supervisor and Professor Anders Sundan as co-supervisor.

Berit Helen Jensen Grandaunet defended her thesis « Bone loss in rheumatoid arthritis: Possible roles for hepatocyte growth factor, syndecan-1 and dickkopf-1» on June 19, 2014 at NTNU, Center of Molecular Inflammation Research (CEMIR) and KG Jebsen Center for Myeloma Research. The experimental work was conducted at the Department of Cancer Research and Molecular Medicine at NTNU with senior research scientist Therese Standal as supervisor and Professors Anders Sundan and Glenn Haugeberg as co-supervisors.

CEMIR OUTREACH ACTIVITIES

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

In 2014, we developed our website further, by better presenting our research environment, facilities and labs for potential collaborators and future personnel. We have also used our website to present news about our activity and research throughout the year.

Media Highlights

In March Marie Austdal was interviewed in the Spanish online on her research on preeclampsia.

In October Egil Lien was interviewed in both Forskning.no and ABC Nyheter about his research on the "Black Death" bacteria.

Trude Flo was interviewed in the national daily paper Verdens Gang (VG) in October, in an article on a new vaccination programme.

Three Phd- students, Ragnhild Skråstad, Marie Austdal og Line Tangeås was interviewed in the local paper Adresseavisa in December on their research on how to analyze and map so-called "dangerous pregnancies".

In February Professor Egil Lien was interviewed about the black death bacteria on Schrödingers katt, NRK1.

BLOGGING In 2014 we wrote several blogs for the #NTNUmedicine blog

IN ENGLISH, 13 BLOG ARTICLES:

- *CEMIR recruits more researchers (Kari Håland)*
- *A new mechanism explaining the anti inflammatory effect (N. Niyonzima and E. Samstad)*
- *Barbara McClintock and todays women in academia (Signe Åsberg)*
- *Cholesterol Crystals induce complement dependent inflammasome activation-and cytokine Release (N.Niynzima and E. Samstad)*
- *Translating Latour back to the laboratory (Kristian Starheim)*
- *Promising new therapeutic strategy for treatment of sepsis (Terje Espevik)*
- *How plague bacteria kill immune cells (Egil Lien)*
- *The black death bacteria continues to kill (Egil Lien)*
- *Could trophoblasts be the immune cells of pregnancy? (G. Stødle og L. Tangeås)*

IN NORWEGIAN, 12 BLOG ARTICLES

- *CEMIR drev vaksinekontor på Barnesykehuset på Forskningstorget (Signe Åsberg)*
- *Du tror det når du får se en infeksjon i tre dimensjoner (Marianne S. Beckwith)*
- *Fredagsforelesning om Inflammasjon: Alle sykdommers mor (Terje Espevik)*
- *24. mars er Verdens tuberkulosedag (Trude Helen Flo)*
- *Hvorfor drar en av verdens mest kjente forskere til Røros i midten av januar? (Magnus Steigedal)*
- *På jakt etter perfekt immunrespons (Trude Helen Flo)*

You can read the blogs here:
http://blog.medisin.ntnu.no/tag/cemir-en/?lang=en

Prøver å finne «farlige» graviditeter

Slik dreper Svartedaudens bakterie fortsatt

Norwegian Science Week - Forskningstorget

CEMIR participated at Forskningstorget, at the main square in Trondheim city center, where researchers meet and communicate their science to the public, especially children. Together with medical students, researchers from CEMIR organized a «teddy bear hospital»

FORSKER GRAND PRIX

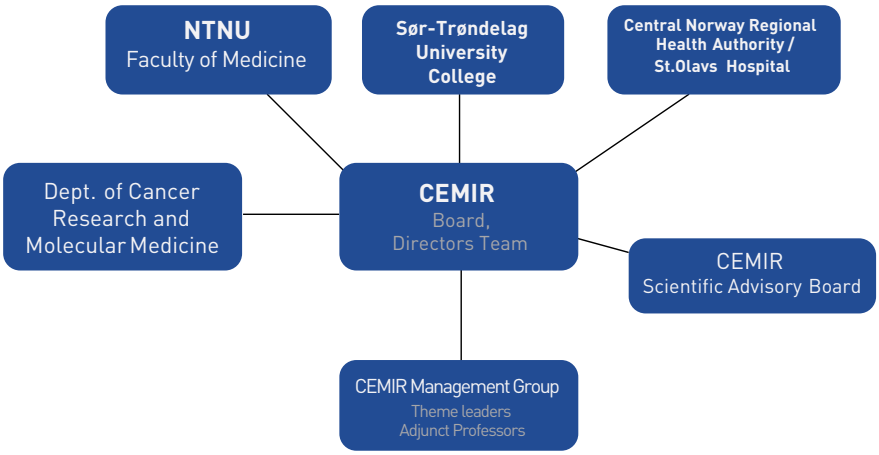
Marianne Beckwith participated in The Researcher Grand Prix, a science communication competition, where each participating PhD candidate has four minutes to present his or her research and engage the audience. A video can be seen here: http://tv.nrk.no/serie/kunnskapskanalen/MDFP15002714/20-12-2014

OTHER OUTREACH ACTIVITY:

In May 2014 CEMIR (Trude Helen Flo) was invited to give a talk about excellence in science to the management of Prestasjonsklyngen. Prestasjonsklyngen is a collaboration between Olympiatoppen, Norsk Ballett og Opera, Accenture and NTNU.

In October Professor Charles Arntzen visited NTNU to talk about the utilization of plant biotechnology for expression of Ebola medicine. CEMIR (Trude Helen Flo) participated in the meetings and presented CEMIR to Arntzen and the Norwegian Biotechnology Advisory Board.

ABOUT CEMIR



CEMIR has two main partners that contribute by performing research activity and providing financing: Sør-Trøndelag University College and The Central Norway Regional Health Authority/St.Olavs Hospital. The centre is closely connected to the host department, Department of Cancer Research and Molecular Medicine at Faculty of Medicine, NTNU. Agreement documents regulate the cooperation with our partners.

The day-to-day management of CEMIR is performed by Director Terje Espevik, Co-Director Trude Helen Flo and Head of Administration Kari Håland. The Centre management reports to the CEMIR board. The centre activities integrate 7 research themes and unite researchers across disciplines for breaking new grounds in inflammation research. In addition 6 international researchers are employed at CEMIR as professor II.

Kari Håland coordinates the administrative operations at CEMIR.

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

CEMIR board

2 board meetings were held in 2014.
The board members are:

- Magne Børset – Board chairman and Head of Dep. of Cancer Research and Molecular Medicine, NTNU
- Stig A. Slørdahl - Dean, Faculty of Medicine, NTNU
- Einar Hjorthol -Dean, Faculty of Technology, Sør-Trøndelag University College (HiST)
- Petter Aadahl - Research director, St. Olavs Hospital
- Anne Borg - Dean, Faculty of Natural Sciences and Technology, NTNU

The function of SAB is to review the scientific progress of the centre and to give guidance to future research directions. A SAB-meeting was held in Trondheim in September 2014. SAB had discussions with the CEMIR management and researchers during their visit, and gave constructive and useful feedback to the CEMIR management. During their visit all members of CEMIR's Scientific Advisory Board held presentations at the annual CEMIR seminar on inflammation

SAB members Douglas Golenbock, Alan Adrem, Göran Hansson and Stefanie Vogel visited CEMIR in September 2014

PRICES AND AWARDS

In May 2014 Katherine Fitzgerald received the esteemed Eli Lilly and Company-Elanco Research Award. Katherine Fitzgerald works as Professor at the University of Massachusetts Medical School, Worcester and Professor II at CEMIR.

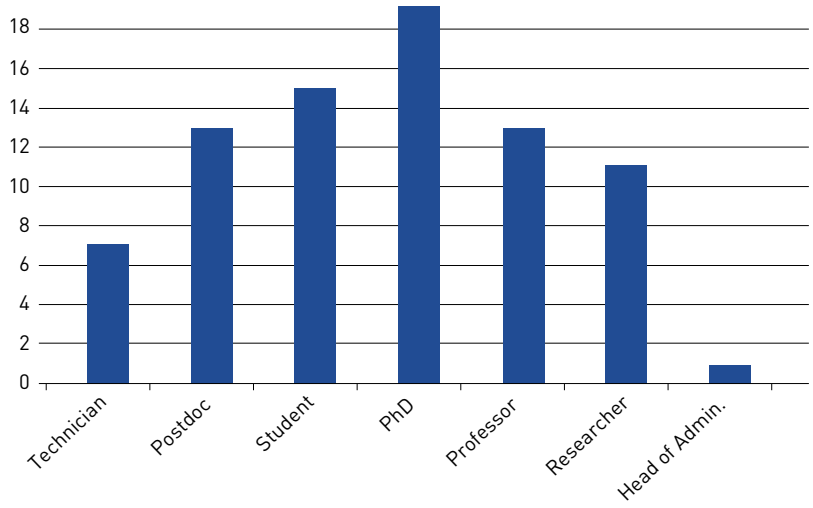
This esteemed prize is awarded to young scientists who have demonstrated outstanding, fundamental research of unusual merit in microbiology or immunology. Research in the Fitzgerald Lab is focused on understanding, in molecular detail, the mechanisms by which the innate immune response recognizes and responds to challenge with pathogenic microbes. "Fitzgerald's research has led to a new understanding of innate immunity, making her a well deserving recipient of this prestigious honor" says Robert Finberg, University of Massachusetts Medical School.

We also congratulate Professor Stenmark with the esteemed award The King Olav V's Cancer Research Award. Harald Stenmark is Professor at Radiumshospitalet, University of Oslo and Professor II at CEMIR. He received the award for his ground-breaking discoveries within cell biology in June 2014.

Stenmark is an expert in the field of intracellular sorting and trafficking mechanisms. The Stenmark Lab studies the molecular mechanisms that promote or suppress cancer, a disease that involves uncontrolled proliferation and invasiveness of specific cell types of the body.

King Olav Vs Cancer Research foundation was established in 1992 by the Norwegian Cancer Society, and since then the Cancer Society has awarded this prestigious prize of 1MNOK annually to Norway's most outstanding cancer researchers.

CEMIR STAFF AND STUDENTS



By the end of 2014 83 people (students included) from 20 different countries were associated with the centre.

Name		Postition	Nationality	Research Group
Andersen	Sonja	Technician	Norway	Autophagy
Anfu	Charles	Master's student	Ghana	Inflammation
Aune	Marie Hjelmseth	Postdoctor	Norway	Inflammation
Austgulen	Rigmor	Professor	Norway	Pregnancy
Awuh	Jane	Postdoctor	Cameroon	Mycobacteria
Bahadro	Marzieh	Master's student	Iran	Autophagy
Bakke	Siril Skaret	Postdoctor	Norway	Inflammation
Beckwith	Marianne	PhD candidate	Norway	Mycobacteria
Bergstrøm	Bjarte	Postdoctor	Norway	Inflammation
Bjørkøy	Geir	Professor	Norway	Autophagy
Boyartchuk	Victor	Researcher	Ukraine	Inflammation
Bugge	Marit	PhD candidate	Norway	Inflammation
Mediaas	Sindre	Med.stud. Research	Norway	Mycobacteria
Damaas	Jan K	Professor	Norway	Inflammation
Dangol	Sristy	Master's student	Nepal	Inflammation
de Jesus	Ramon Carl	Master's student	Norway	Inflammation
Dragset	Marte Singsås	Postdoctor	Norway	Mycobacteria
Egeberg	Kjartan	Technician	Norway	Inflammation
Espevik	Terje	Professor	Norway	Inflammation
Fitzgerald	Kate	Professor II	USA	
Flo	Trude Helen	Professor	Norway	Mycobacteria
Gidon	Alexandre	Postdoctor	France	Mycobacteria
Gierman	Lobke	Postdoctor	Netherlands	Pregnancy
Ginbot	Zekarias	Researcher	Eritrea	Mycobacteria
Gjerdingen	Thea	Master's student	Norway	Inflammation
Granlund	Atle Van Beelen	Postdoctor	Norway	IBD
Grøvdal	Lene Melsæther	Postdoctor	Norway	Inflammation
Haug	Markus	Researcher	Germany	Mycobacteria
Helland	Maja	Master's student	Norway	Mycobacteria
Husebye	Harald	Researcher	Norway	Inflammation
Håland	Kari	Head of admin.	Norway	
Ibrahim	Hany	PhD candidate	Egypt	Mycobacteria
Iversen	Ann-Charlotte	Associate Professor	Norway	Pregnancy
Johansson	Ida	PhD candidate	Norway	Autophagy
Kannan	Nisha	PhD candidate	India	Mycobacteria
Kojen	June Frengen	Technician	Norway	Inflammation
Kumashie	Kingsley Gideon	Master's student	Ghana	Mycobacteria
Latz	Eicke	Professor II	Germany	
Lien	Egil	Professor II	Norway/USA	
Louet	Claire	Technician	France	
Marstad	Anne	Researcher	Norway	Mycobacteria
Mildenberger	Jennifer	PhD candidate	Germany	Autophagy
Mollnes	Tom Eirik	Professor II	Norway	
Neckmann	Ulrike	PhD candidate	Germany	Autophagy

Name		Postition	Nationality	Research Group
Nilsen	Nadra	Researcher	Norway	Inflammation
Niyonzima	Nathalie	PhD candidate	Burundi	Inflammation
Nonstad	Unni	Technician	Norway	Inflammation, autophagy
Nur	Muhammad	Master's student	Bangladesh	Inflammation
Patané	Francesco	PhD candidate	Italy	Inflammation
Paulsen	Julie	PhD candidate	Norway	Inflammation
Pettersen	Kristine	PhD candidate	Norway	Autophagy
Ramberg	Oda Helgesen	Master's student	Norway	Mycobacteria
Rokstad	Anne Mari	Researcher	Norway	Inflammation
Ryan	Liv	Researcher	Nepal	Mycobacteria
Samstad	Eivind	PhD candidate	Norway	Inflammation
Sandvik	Arne	Professor	Norway	IBD
Schrøder	Ida Caroline	Master's student	Norway	Mycobacteria
Silva	Gabriela Brettas	PhD candidate	Brazil	Pregnancy
Siyum	Yohannes Derese	Master's student	Ethiopia	Mycobacteria
Skei	Bente	Technician	Norway	Pregnancy
Skjesol	Astrid	Postdoctor	Norway	Inflammation
Skovdahl	Helene Kolstad	Med.stud. Research	Norway	Inflammation
Solli	Helene	Master's student	Norway	Inflammation
Standal	Therese	Professor	Norway	Bone disease
Starheim	Kristian K.	Postdoctor	Norway	Inflammation
Steigedal	Magnus	Researcher	Norway	Mycobacteria
Steinkjer	Bjørg	Technician	Norway	Inflammation
Stenmark	Harald	Researcher	Norway	Inflammation
Stenvik	Jørgen	Researcher	Norway	Inflammation
Stødle	Guro	PhD candidate	Norway	Pregnancy
Sundan	Anders	Professor II	Norway	Bone disease
Tangerås	Line	PhD candidate	Norway	Pregnancy
Thorsvik	Silje	PhD candidate	Norway	IBD
Underhill	David	Professor II	USA	
Vik	Randi	Technician	Norway	Inflammation
Waagsbø	Bjørn	PhD candidate	Norway	Inflammation
Wilson	Ernest	Master's student	Ghana	Mycobacteria
Yurchenko	Mariia	Postdoctor	Ukraine	Inflammation
Zahoor	Muhammad	Postdoctor	Pakistan	Bone disease
Ørning	Mathias Pontus	PhD candidate	Sweden	Inflammation
Østvik	Ann Elisabeth	Postdoctor	Norway	IBD
Åsberg	Signe	PhD candidate	Norway	Mycobacteria

RESULTS 2014:
PUBLICATIONS, THESIS AND ACADEMIC PRESENTATIONS

JOURNAL PUBLICATIONS

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ACADEMIC PRESENTATIONS

Aune, Marie Hjelmseth. Inflammasjon og helse. Forsker til lunsj; 2014-09-17, NTNU

Aune, Marie Hjelmseth; Samstad, Eivind; Niyonzima, Nathalie; Nymo, Stig Haugset; Ryan, Liv; Lappegård, Knut Tore; Brekke, Ole Lars; Lambris, John D.; Damås, Jan Kristian; Latz, Eicke; Mollnes, Tom Eirik; Espevik, Terje. Cholesterol crystals induce complement-dependent inflammasome activation. NBS Contact Meeting; 2014-01-23 - 2014-01-25, NLSH NTNU UiO UiT

Austdal, Marie; Tangerås, Line; Skråstad, Ragnhild; Salvesen, Kjell Å; Austgulen, Rigmor; Iversen, Ann-Charlotte; Bathen, Tone Frost. First trimester urine and serum NMR metabolomics to predict preeclampsia and gestational hypertension. Metabomeeting 2014; 2014-09-09 - 2014-09-12, NTNU

Austdal, Marie; Tangerås, Line; Skråstad, Ragnhild; Salvesen, Kjell Å; Austgulen, Rigmor; Iversen, Ann-Charlotte; Bathen, Tone Frost. First trimester urine and serum NMR metabolomics to predict preeclampsia. The 2014 Joint National PhD Conference in Medical Imaging and MedViz conference; 2014-06-17 - 2014-06-18, NTNU

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Beckwith, Marianne. Aclar microwells for Correlative Imaging of Mycobacterium infected Macrophages by CLSM and FIB/SEM. SCANDEM 2014; 2014-06-09 - 2014-06-13, NTNU

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Beckwith, Marianne. Du tror det når du får se det: en infeksjon i tre dimensjoner. Forsker grand prix Trondheim; 2014-09-25 - 2014-09-25, NTNU

Beckwith, Marianne. Optimizing Correlative Imaging of Mycobacterium-infected Macrophages by CLSM and FIB/SEM. Norwegian Biochemical Society (NBS) Contact Meeting 2014; 2014-01-23 - 2014-01-26, NTNU

Beckwith, Marianne; Beckwith, Kai Sandvold; Sikorski, Pawel; Flo, Trude Helen; Halaas, Øyvind. Correlative imaging by light microscopy and FIB/SEM tomography. NTNU NanoLab 10 Year Anniversary; 2014-11-10 - 2014-11-11, NTNU

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Espevik, Terje. Cholesterol crystals induce inflammation: how does it happen and why does it matter?. Research Institute of Internal Medicine seminar; 2014-03-27 - 2014-03-27, NTNU

Espevik, Terje. Inflammasjon: Alle sykdommers mor. Fredagsforelesning St. Olavs Hospital; 2014-05-16 - 2014-05-16, NTNU

Espevik, Terje. Inflammatory responses induced by cholesterol crystals. 11th International Conference on Innate Immunity; 2014-06-01 - 2014-06-01, NTNU

Espevik, Terje. Mechanisms involved in the induction of IFN-b by Gram negative- and Gram positive bacteria. Seminar; 2014-06-27 - 2014-06-27, NTNU

Espevik, Terje. TLR4/TRAM trafficking mechanisms involved in the IFN-b response induced by E.coli. Seminar; 2014-07-26 - 2014-07-26, NTNU

Espevik, Terje. Toll-like receptor 4 signalling from the endosome. Europeat Tissues Repair Society meeting; 2014-09-11 - 2014-09-11, NTNU

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FUNDING AND EXPENDITURES 2014

Funding (1000 NOK)	2014
NTNU	12 599
Research Council of Norway (RCN) – Centre of Excellence grant	13 774
Other RCN funding	8 214
Other public funding	11 934
Other privat funding	1 885
Total funding	**48 406**

Expenditures (1000 NOK)	2014
Personnel and indirect costs	38 974
Equipment	1 664
Other operating costs	7 768
Total expenditures	**48 406**

Microscopy photos:
Page 5, 7 : Bjørnar Sporsheim, CMIC
Page 6: Egil Lien, CEMIR
Page 8: Marianne S. Beckwith, CEMIR
Page 9: Guro Stødle, CEMIR
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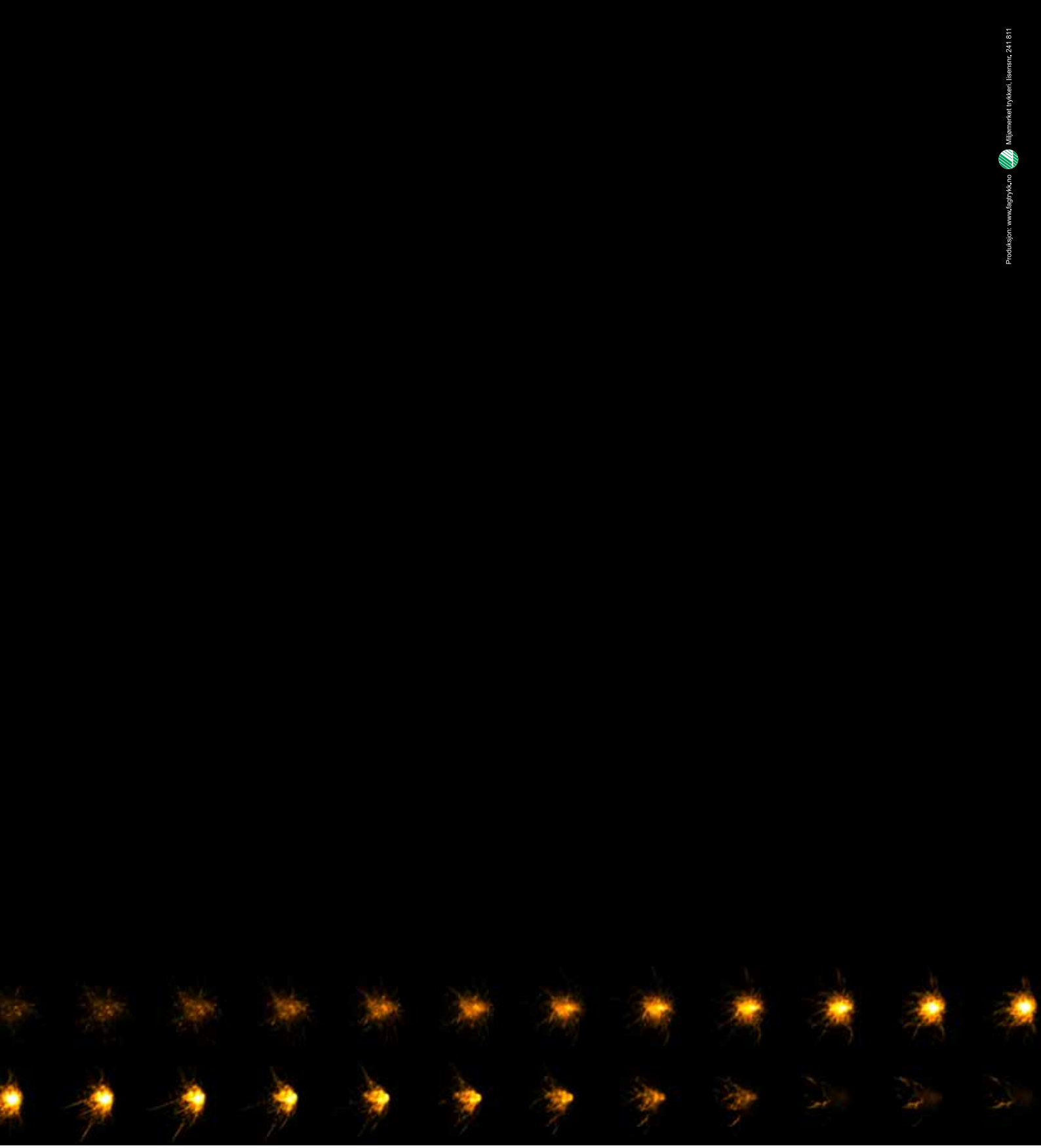

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