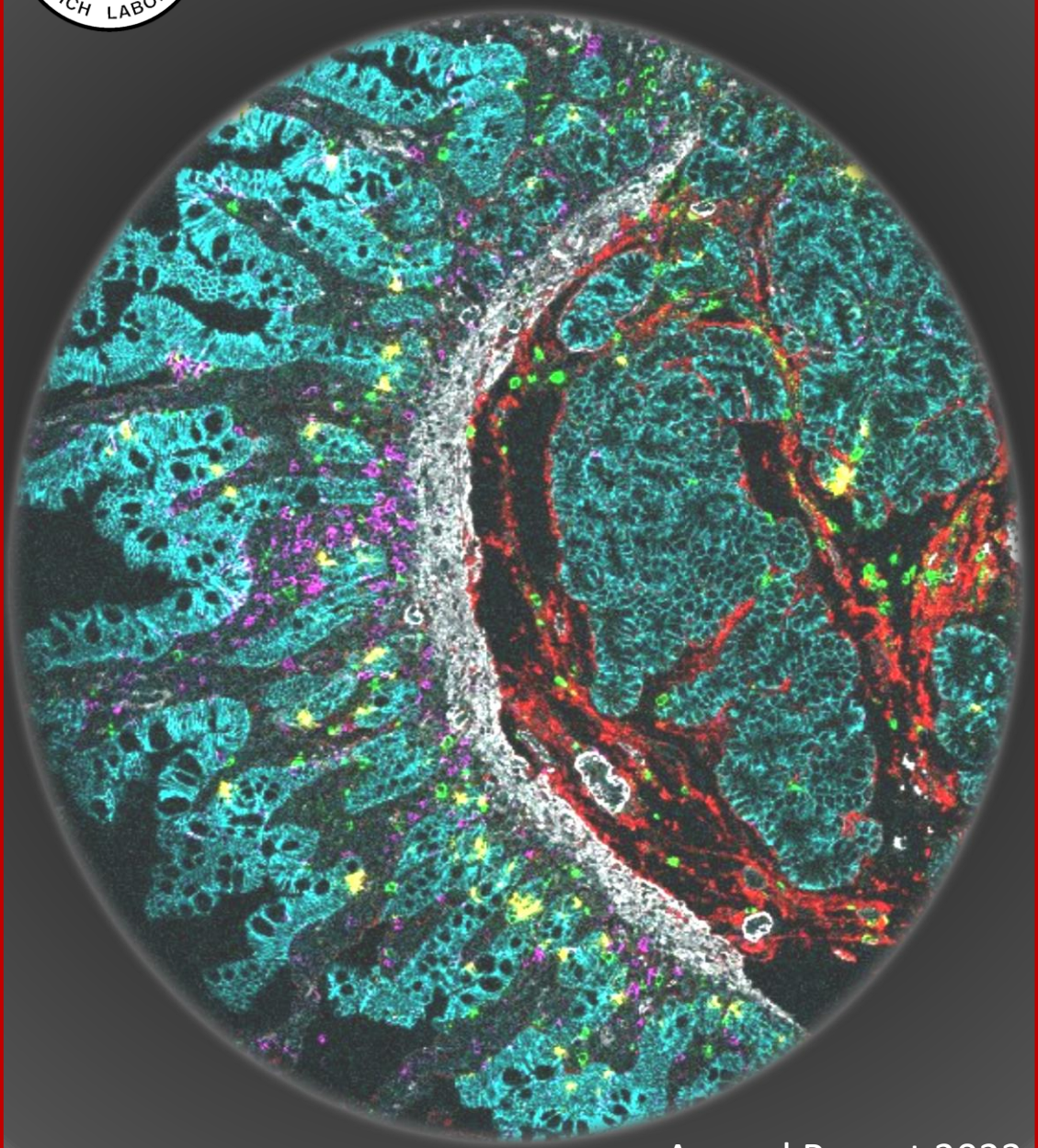
Broegelmann Research Laboratory

University of Bergen



Annual Report 2023

HIGHLIGHTS

7
New group members

2
New graduates

26
Published articles

2
New Grants

60
Research School students

3
Invited international speakers

CONTENT

Editors: Richard Davies and Helena Erlandsson Harris

Photographers: Marta Kaminska, Silke Appel, Helena Erlandsson Harris, Harini Pechiappan, Richard Davies, Stefan Bladh

Front cover picture: by Aina van der Meeren, duodenum,
image by Hyperion imaging mass cytometry system. Key- white: smooth muscle actin, teal: epithelial cells, green: mast cells, yellow: enterochromaffin cells, red: Collagen I, purple: CD8 T cells.

DIRECTOR'S COMMENTS

Helena Erlandsson Harris, PhD.
Head of Broegelmann Research Laboratory, 2023

'' As the new head of the Broegelmann Research Laboratory I have the goal, together with all BRL researchers, to further develop BRL as a hub for research on inflammatory diseases. And ensure that the tradition of translational immunological research is continued and expanded by utilising the modern, state-of-the-art facilities available at UiB. Not only is this important in the quest to improve treatment and care of those affected by chronic inflammatory conditions, it is also the foundation for high quality doctoral education ''.

These were my visions in January 2022, and they are still valid. Therefore, it is with pride that I present to you the 2023 Annual report for the Broegelmann Research Laboratory. It is a summary of our endeavors during 2023 and a testament that we are striving towards my vision. As clearly indicated by the highlights, we have continued both a steady output of scientific articles in international, renowned scientific journals and to educate an impressive number of students at both undergraduate and graduate levels. All made possible through the talented and dedicated work by the members of the BRL. Step by step consolidating and realizing my vision.

We were visited by international guest lecturers, including Peder Olofsson, Karolinska Institutet, who gave this year's Broegelmann lecture. Peder shared his knowledge in bioelectronic medicine, a scientific field of high relevance for chronic inflammatory diseases and the development of new therapeutic strategies. Listening to invited speakers and having the opportunity to discuss with them, as well as actively participating at international conferences, is inspiring and provides good opportunities for new collaborations. This has certainly been the case during 2023 and I look forward to seeing the results in the years to come.

We accepted 5 Master students to the laboratory which has been fruitful both regarding the science produced and from an education perspective. I am also proud that Aleksandra Petrovic successfully defended her doctoral thesis on the immunopathogenesis of psoriasis, a good example of the translation approach we embrace at the BRL.
More on our achievements and some personal portraits from BRL can be found in the annual report.

I hope you enjoy the reading!

Helena Erlandsson Harris,
Head of Broegelmann Research Laboratory

Vision and Research Areas

''To pave the way for personalized treatment and ultimately prevention of rheumatic diseases and their associated co-morbidities''

The researchers at the Broegelmann Research Laboratory have a mutual interest in translational research on chronic inflammatory and autoimmune diseases. The research performed spans from molecular and genetic studies, cellular studies and experimental models as well as studies on clinically well-characterized patient samples.

The mutual ambition is to understand the molecular mechanisms active in different inflammatory diseases and their subgroups, their underlying risk factors and triggers. This paves the way for better, personalized treatment and ultimately to prevention of disease.

Current major areas of research:

Translational studies in autoimmunity; autoantibodies and biomarkers

Immunopathogenesis of juvenile idiopathic arthritis

Role of HMGB1 in inflammation

Functional genomics and genetic basis of the autoimmune exocrinopathy (Sjögren's syndrome)

Host microbe interactions (*P. gingivalis* – arthritis, Alzheimer)

Hyperinflammatory primary immunodeficiency syndromes

Novel natural product based COVID-19 therapy

Intestinal mucosal microenvironment in irritable bowel syndrome

Our groups and members

BRL is composed of several groups lead by principal investigators (PIs). Group members are recruited throughout the world and share a focus for understanding and improving treatment of rheumatic diseases

Group and PI profiles

Yenan Bryceson

Yenan Bryceson did his undergraduate training at the University of Oslo and PhD at the National Institutes of Health, Rockville, MD, USA. He was appointed professor II at the University of Bergen in 2012. He is also a professor at Karolinska Institutet, Stockholm, Sweden.

Yenan's group studies the molecular regulation of cytotoxic lymphocyte function in the context of inflammatory disease as well as cancer. Defects in cytotoxic lymphocyte function are associated with often fatal hyperinflammatory primary immunodeficiency syndromes in infants, but many such patients cannot be explained by current molecular insights. Furthermore, harnessing lymphocyte differentiation and function represents a promising avenue increasing the efficacy of cellular immunotherapy of cancer.

Their group focuses on the molecular regulation of cytotoxic lymphocyte function in inflammation. Cytotoxic lymphocytes are broadly categorized into cytotoxic CD8+ T cells and natural killer (NK) cells. Defects in cytotoxic lymphocyte function are associated with often-fatal hyperinflammatory primary immunodeficiency syndromes in infants. These hyperinflammatory syndromes are also associated with an increased risk of developing hematological malignancies.

Recently, adoptive transfer of NK cells or T cells engineered to express chimeric activating receptors (CARs) have shown efficacy in clinical trials against hematological malignancies, but improving their persistence and potential utility against solid tumors remains a major challenge.

They are working to decipher the molecular regulation of cytotoxic lymphocyte differentiation and function in blood and tissues using cutting-edge single cell techniques, including advanced flow cytometry and sorting combined with high-throughput sequencing. A particular focus of theirs is on how specific transcription factors can be harnessed to manipulate NK cell differentiation and potentiate function for improved immunotherapy of cancer.

Helena Erlandsson Harris

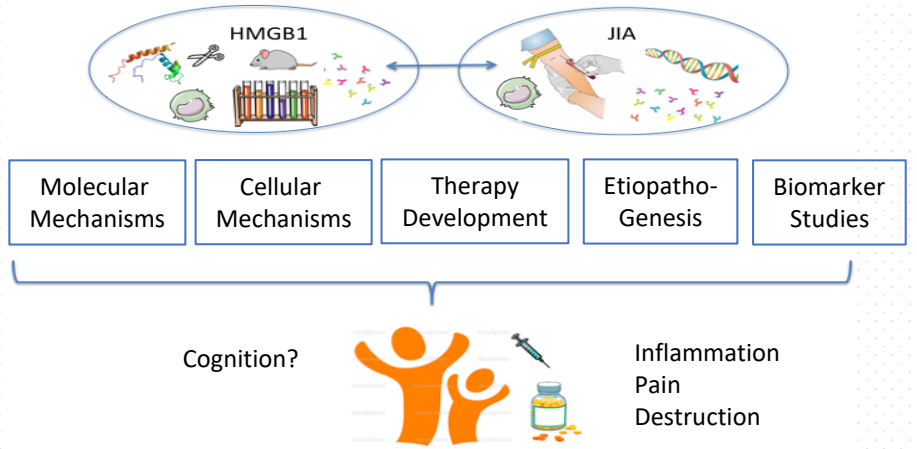
Helena Erlandsson Harris did her undergraduate training at the University of Uppsala and PhD at the Karolinska Institutet, Sweden. She was appointed professor at Karolinska institutet in 2014. She became head of the Broegelmann Research Laboratory and Professor in Immunology at the University of Bergen in 2022.

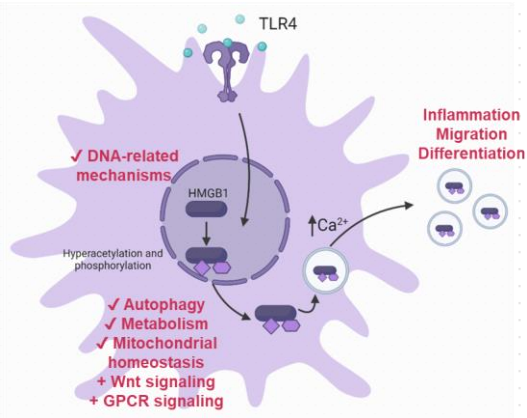
Juvenile idiopathic arthritis (JIA) is chronic arthritis affecting children. There is a great need for improved diagnostic and prognostics tools as well as new therapeutic options. In addition to joint inflammation, destruction of joint tissue and pain are hallmarks of the disease. In depth understanding of the molecular mechanisms driving these three hallmarks forms the basis for development of diagnostic/prognostic biomarker tests as well as development of new, specific therapy – precision medicine.

Alarmins are endogenous molecules released from stressed and dying cells with the function to initiate an inflammatory response. Helenas group studies the alarmin HMGB1, how it can induce cell migration, cytokine production, cell differentiation and regeneration. All important features of chronic inflammation, including arthritis.

Their projects are focused on expanding the molecular knowledge of the immune mechanisms active in JIA as a basis for biomarker and therapy development. To achieve this they analyse biosamples collected from children with JIA and compare generated data with information retrieved from national quality registers. In a recently started project they are investigating the possible connection of JIA, neuroinflammation and its potential influence on quality of life.

How HMGB1 is contributing to inflammation, pain and destruction is studied with a translational approach using molecular and cellular functional studies, analyses of HMGB1 in patient samples and model systems.





Marie Wahren-Herlenius

Marie Wahren-Herlenius did part of her PhD training and a postdoctoral period at the Broegelmann Research Laboratory. She was appointed professor II, University of Bergen in 2020. She is also a professor at Karolinska Institutet, Stockholm, Sweden.

The majority of autoimmune diseases are more common in women than in men, but the molecular basis for this sex-bias remains poorly understood. Marie's projects focus on the autoimmune exocrinopathy Sjögren's syndrome which has among the highest observed female-to-male ratios, to dissect the genetic and hormonal contribution to sex-dependent immune regulation at single cell resolution and how these differences may lead to autoimmune disease.

Women are at much higher risk of developing autoimmune disease, with the most extreme numbers in systemic disorders such as SLE and Sjögren's syndrome for which more than nine out of ten patients are women. There is a clear genetic contribution to these diseases and genome-wide studies have identified polymorphisms associated with Sjögren's syndrome. Interestingly, many of the associated genetic variants lead to differential gene regulation. However, the influence of sex, or why these immune-pathways and related genes would become dysregulated specifically in women is not clear.

In their projects, they build on the observation that genetic polymorphisms associated with Sjögren's syndrome that we identify dramatically increase the likelihood for the disease to develop in women carrying these genetic traits compared to men. Consequently, the context "female sex" may lead to a different functional impact of the genetic polymorphisms associated with systemic autoimmunity than the context "male sex". Their projects aim to identify sex-influenced eQTLs, and dissect the genetic and hormonal contribution to sex-dependent immune regulation at single cell resolution and how these differences may lead to autoimmune disease.

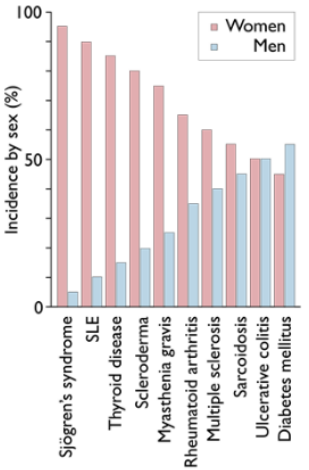


Figure 1. Sex distribution of the major Autoimmune diseases.

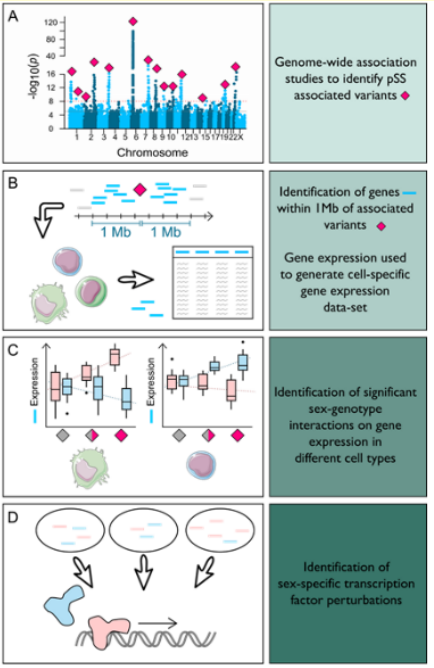


Figure 2. Steps to identify sex-influenced eQTLs and their mechanistic basis.

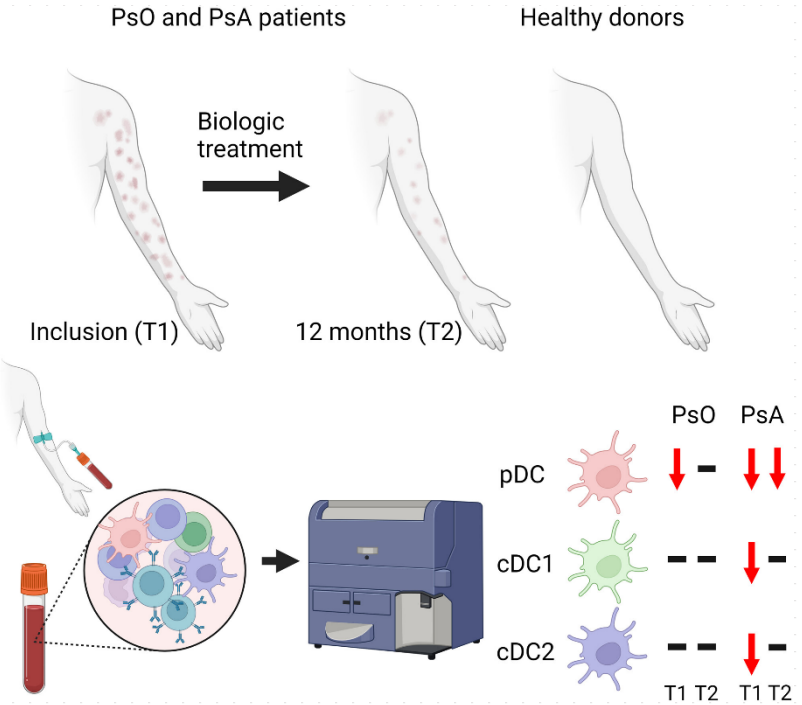
Silke Appel

Silke Appel did her PhD at the Max-Delbrück Center for Molecular Medicine, Germany followed by post-doctoral work at the Universitätsklinikum Tübingen, Germany and the University of Bergen. She was awarded the Trond Mohn Starting Grant 2007, She was appointed professor at the University of Bergen in 2012. She is head of Research at the Department of Clinical Science and head of the core facility for flow cytometry.

Single cell network profiling of distinct immune cells allows analyzing pathway specific activity of patient samples at the single cell level. This will enable the stratification of different categories of patients and develop personalized therapies. The overall aim of their research is to further unravel the mechanisms by which dendritic cells modulate T cell responses in autoimmunity. Their results will lead to a better understanding of the cellular mechanisms involved in antigen presentation, T cell stimulation and tolerance induction, thereby revealing new tools for diagnosis and targets for therapy of patients with cancer, autoimmune and infectious diseases as well as patients undergoing stem cell transplantation. Thus, it will lead to an increased survival and better quality of life for patients.

During the past year, they have used multi-color flow cytometry to show that patients with psoriasis have alterations in their dendritic cell populations (Petrovic et al., Scand J Immunol, 2023). Moreover, they observed some beneficial effects using herring roe oil in the treatment of patients with mild to moderate psoriasis (Petrovic et al., Front Immunol, 2023).

In collaboration with professor Torgils Fossen at the Department of Chemistry, they have established a screening system to test anti Sars-CoV2 activity of phytochemicals with promising results.
Another focus of the group is Sjögren's disease. They have established a 36-antibody panel to collect spatial information of various immune cells in salivary glands of these patients for better stratification and to improve diagnostics and treatment.



Patients with psoriasis vulgaris without (PsO) or with psoriatic arthritis (PsA) show alterations in peripherial blood dendritic cell (DC) populations. Pertrovic et al. 2023.

Piotr Mydel

Piotr Mydel did his PhD education at the Jagiellonian University in Krakow, Poland and at the University of Boston, MA, USA followed by post-doctoral work at Washington University, University of Gothenburg and University of Bergen. He was appointed Professor I at the University of Bergen in 2019. Piotr Mydel also holds a professorship at the Jagiellonian University.

The group believes in interdisciplinary cooperation with medical and dental clinicians, epidemiologists, bio-scientists, industrial scientists to achieve their goals of elucidating the role of post-translational modifications in the aetiology of auto-immune diseases.

Taking into account that up to 30% of the adult population worldwide suffers from severe periodontitis, the impact of this disease on human health is immense. Periodontitis (PD) is largely caused by infection, in which Porphyromonas gingivalis is a major pathogen, and is the most prevalent infectious inflammatory disease of mankind.

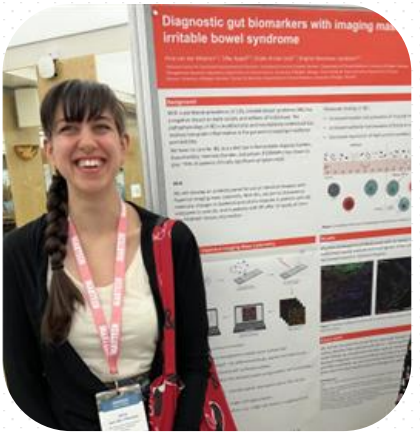
Mounting evidence suggests a causative link between PD and rheumatoid arthritis (RA), as well as periodontitis and cardiovascular disease. P. gingivalis is the only bacterium expressing the enzyme peptidylarginine deiminase (PAD) which converts arginine to citrulline, a process referred to as citrullination. Antibodies towards such citrullinated proteins, i.e ACPAs/anti-CCP, are of central importance in RA a chronic autoimmune disease which affect 0.5-1% worldwide. The presence of ACPAs or anti-CCP autoantibodies is not only highly specific for RA but the presence is also related to a more severe and destructive disease progression.

They hypothesise that anti-citrullinated protein antibodies can be generated, in genetically susceptible individuals, as a consequence of P. gingivalis-induced citrullination in the gingiva.

Highlighted member profiles

Noemie Dudzinska from Poland, joined as a PhD candidate in 2022 in Piotr Mydel's group.
What are you working on? I am investigating the role of *Porphyromonas gingivalis* and its virulence factors on the nervous system, aiming to mechanistically link the incidence of periodontitis and neurodegenerative diseases such as Alzheimer's disease.
What does your week consist of? A bit of everything. I have lab work, data analyses, meetings within the group, meetings with collaborators or other PhD candidates from other groups.
What inspired you to pursue a career in science? My ingrained need is to constantly develop, get better, challenge myself and seek what is important.
What is your favorite aspect of your work? That I have access to what big public has no access to: detailed knowledge about specific topics. I feel privileged.
If you could compare yourself to an animal, what would it be and why? I am like a giraffe as I can reach what is unreachable for others.

Aina van der Meeren from Norway, joined as a PhD candidate in 2022 in Silke Appel's group.



What are you working on? I'm working on intestinal low-grade inflammation and increased intestinal permeability in irritable bowel syndrome (IBS). I investigate duodenal and colonic biopsies with Hyperion imaging mass cytometry before and after a strict 12-week low FODMAP diet.

What does your week consist of? My weeks vary. When I have lab work, I usually spend two consecutive days in the lab, since my protocols often require overnight staining. I have some weekly meetings and seminars. Nowadays I spend much time data wrangling and banging my head against the R (a statistical program) wall.

What inspired you to pursue a career in science? The initial spark was lit in my early teens, reading several of Lurlene McDaniels young adult books about adolescents facing serious illness. I later took an interest in natural sciences in school and decided to study molecular biology (after a couple of detours into other fields).

What is your favorite aspect of your work? It's hard to choose, there's much about my work I like. I enjoy the variation and flexibility of it, and like the combination of lab and computer work. I appreciate the possibility to travel to conferences and see new places. I love the people!

If you could compare yourself to an animal, what would it be and why? I'm a squirrel. Organised, slightly neurotic, with a love for nature and an emergency stockpile at home.

Marta Kaminska from Poland works as a postdoc and project manager in Piotr Mydel's group. She runs the course HUIMM901 and the popular academics anonymous, a platform for junior researchers to discuss life as a researcher.

What are you working on? My scientific interests are post-translational modifications, vasculature and host-pathogen interactions. As of now, I've just begun my project on the links between periodontitis and Alzheimer's disease, where I'll be employing imaging mass cytometry. Very exciting!

What does your week consist of? My weeks have two categories: either a writing week, or laboratory week. You can guess why. In between these tasks, I'm trying to be prolific about my e-mail correspondence (I really don't like to have "unread" emails), as well as checking-in on Piotr's group and making sure that everyone is supported, and some progress is being made.

What inspired you to pursue a career in science? I was always curious about nature and how things work. I made the decision to go into molecular biology in high school when I got fascinated by Mendel's experiments.

What is your favorite aspect of your work? That is really hard for me to say, because I like most aspects of my work. But my absolute favorite is probably doing new things be it a new method I'm learning, or new project I'm trying to come up with and coherently describe.

If you could compare yourself to an animal, what would it be and why? A cat - walking my own path, observing birds and midday naps.

Harini Pechiappan (left) from India joined as a PhD candidate in 2022 and **Bram van Gaans** (right) from the Netherlands as an intern in 2023, both in Helena Harris's group.

What are you working on? Harini: Functional and biological studies of HMGB1 (high mobility group box 1) dimerization, focusing on their active secretion and in what form they are released (monomers, dimers or complexes). **Bram:** Characterizing functional variants of the prototypical alarmin HMGB1 to gain more insight in its role in inducing inflammation.

What does your week consist of? Harini: Routine cell cultures! Mostly, I run gels and do western blot (which is complete fun 😊), and occasionally ELISA! I try to organise some reading at least an article a day.

Bram: My week usually consists of a mix between attending meetings, writing, and being busy in the lab.

What inspired you to pursue a career in science? Harini: I'm drawn to understanding the world around us and uncovering its mysteries. Science provides the tools to explore, discover, and make sense of it all!

Bram: Because of the challenges it gives, while also allowing me to continuously learn and provide knowledge to others.

What is your favorite aspect of your work? Harini: I enjoy trying new things which help to answer the complex research questions we ask ourselves every day! And working in a research group with amazing brains! **Bram:** Discovering potentially novel findings and discussing them with my colleagues.

If you could compare yourself to an animal, what would it be and why?

Harini: Chameleon. As they adapt to their environment, I adapt to the needs and preferences of those I interact with, blending in to provide the most fitting responses and assistance. It absolutely helps to survive in any tough environment 😊 **Bram:** It'll probably be something like a mountain goat, considering I like climbing and the mountains, so why not.

BRL MEMBERS

Head of Laboratory

Helena Erlandsson Harris, PhD (prof I)
Head of Bergen research school of inflammation.
(inflammation/rheumatology)

Academic staff

Piotr Mydel, MD, PhD (prof I)
(biochemistry/immunology)

Silke Appel, Dr. rer. nat. (prof I)
(cellular/molecular immunology)

Marie Wahren-Herlenius, MD, PhD (prof II) *(rheumatology/immunology)*

Yenan Bryceson, PhD (prof II)
(cellular/molecular immunology)

Roland Jonsson, DMD, PhD (prof emeritus) *(rheumatology/immunology)*

Janka Babickova, PhD (researcher)
(biochemistry/nephrology)

Tim Holmes, PhD (researcher)
(cellular/molecular immunology)

Valentyn Oksenych, PhD (researcher)
(cellular/molecular immunology)

Marta Kaminska, PhD (post doc)
(biochemistry)

Trainees
(supervisors in parentheses)

Aina van der Meeren, PhD candidate
(Berentsen Jacobsen/Appel/ Lied)

Aleksandra Petrovic, PhD candidate
(Appel/Jonsson (Roland)/Solberg)

Dorentina Osmani, PhD candidate
(Fossen/Appel/Kaminska)

Harini Pechiappan, PhD candidate
(Erlandsson Harris/Jonsson (Maria)/Aulin/Davies)

Noemi Dudzinska, PhD candidate
(Mydel/Kaminska)

Urszula (Ula) Kalucka, PhD candidate
(Mydel/Appel/Kaminska)

Alireza Molai, MSc student (Pharmacy)
(Appel/Bergum/Borge)

Sigrid Strätveit Gravning, MSc student (Pharmacy)
(Erlandsson Harris/Pechiappan)

Stine Hellestø, MSc student (Pharmacy)
(Osmani/Appel/Fossen)

Yosief Debessai Micheal, MSc student (Pharmacy)
(Mydel/Kaminska)

Annika Øye Guddal, Research line (Dentistry)
(Appel/ Skarstein / Erlandsson Harris)

Bram Van Gaans, Intern
(Erlandsson Harris/Davies)

Technical and administrative staff

Beate Andersen, office manager

Kjerstin Jakobsen, lab manager

Marianne Eidheim, lab manager

Richard Davies, PhD, senior lab manager

ADDITIONAL SCIENTISTS/ KEY-COLLABORATORS AT UIB AFFILIATED WITH THE LABORATORY

Erik Johnsen, Professor
Department of Clinical Medicine

Hans Peter Marti, Professor
Department of Clinical Medicine

Johan G. Brun, Professor
Haukeland University Hospital

Kathrine Skarstein, Professor
Department of Clinical Medicine

Malin V. Jonsson, Professor
Department of Clinical Dentistry

Rebecca Cox, Professor
Department of Clinical Science

Torgils Fossen, Professor
Department of Chemistry

Stephanie Le Hellard, Professor
Department of Clinical Science

Birgitte Berentsen Jacobsen,
Assoc Professor
Department of Clinical Medicine
Haukeland University Hospital

Lene Frøyen Sandvik, Assoc Professor
Haukeland University Hospital

Rune Kroken, Assoc Professor
Department of Clinical Medicine

Silje Solberg, Assoc Professor
Haukeland University Hospital

Daniel Hammenfors, MD, PhD
Haukeland University Hospital

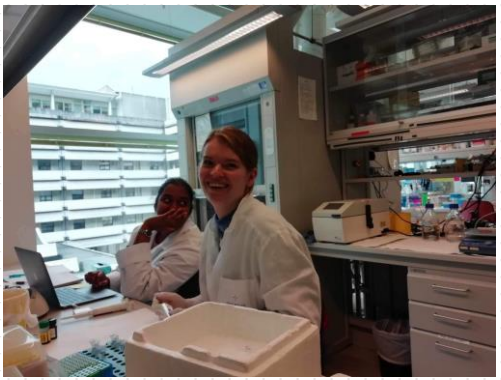
Maria K. Jonsson, MD, PhD
Haukeland University Hospital

Brith Bergum, PhD
Department of Clinical Science

Jørn Skavland, PhD
Department of Clinical Science

New members autumn

Xmas lunch



Lab fun with Harini and Sigrid

Summer party

Deadlines with Tim

Silke and Beate

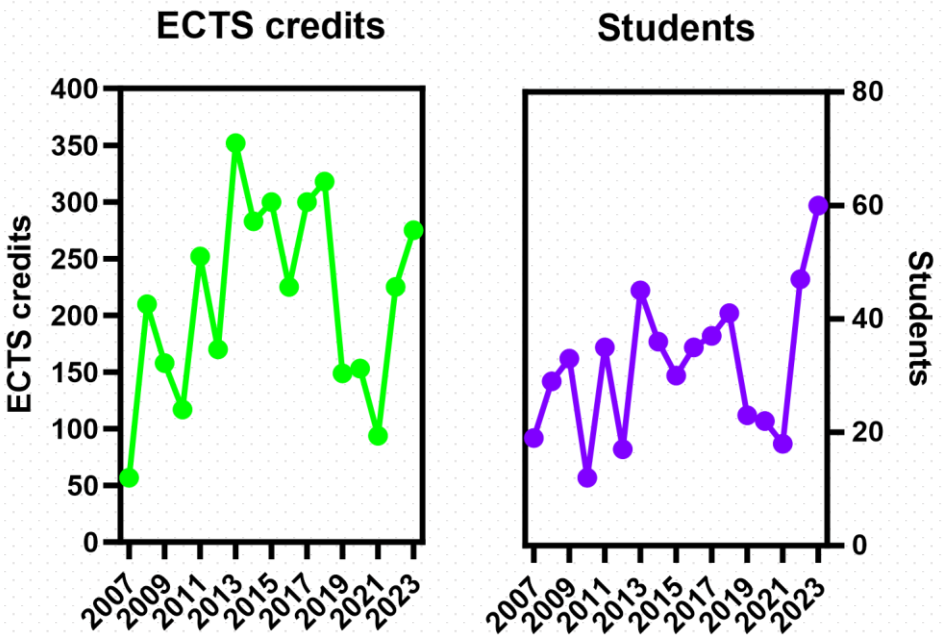
Education

Understand and treating disease is a multigeneration endeavor. A core focus of BRL is training the next generation of researchers. Training is facilitated through the Bergen Research School in Inflammation and the recruitment of trainees, with trainees and staff from BRL actively involved in teaching

Bergen Research School in Inflammation (BRSI)

BRSI, headed by Helena Erlandsson Harris and coordinated by Richard Davies, is open to PhD candidates at UiB and encompasses activities such as courses, seminars, journal clubs – all with the aim to provide subject-specific knowledge to the participants. Furthermore BRSI is an important platform for the interaction between PhD candiates and experienced scientists, to build networks, provide input on research projects and facilitate informal mentoring on research careers.

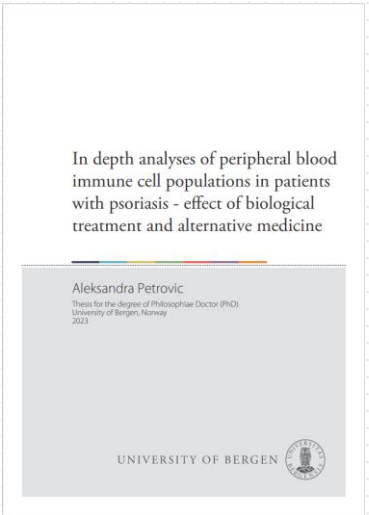
Following a drop in student numbers during the Covid pandemic, student participation in the research school peaked in 2022 and 2023.



BRSI courses given during 2023

- **HUIMM320** Basic Immunology (5 ECTS) – Introduction to modern, basic human immunology
- **HUIMM307** Basic course in Flow Cytometry (5 ECTS) – Practical course with a basic introduction to flow cytometry
- **HUIMM901** Project seminars in immunology (3 ECTS) – Seminars by guest scientists and progress reports by PhD fellows and postdocs
- **HUIMM902** Journal club and watch (3 ECTS) – Series of meetings in which a research paper, its methods, and findings are presented to a group of colleagues
- **HUIMM306A/906A** Molecular and Cellular Methods in Immunology (8 ECTS) – Practical course introducing the basic methods used in immunological research

BRL graduations 2023

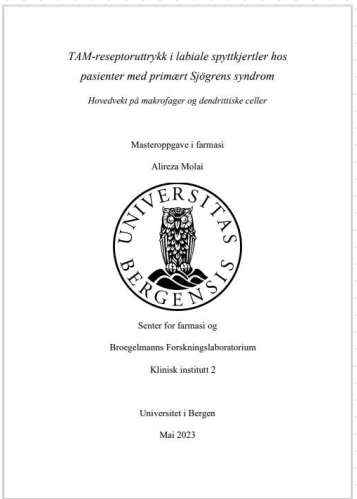


Aleksandra Petrovic

Supervisors:

Silke Appel, Roland Jonsson

Philosophiae doctor, April 26, 2023



Alireza Molai

Supervisors:

Silke Appel, Brith Bergum, Hanne Borge

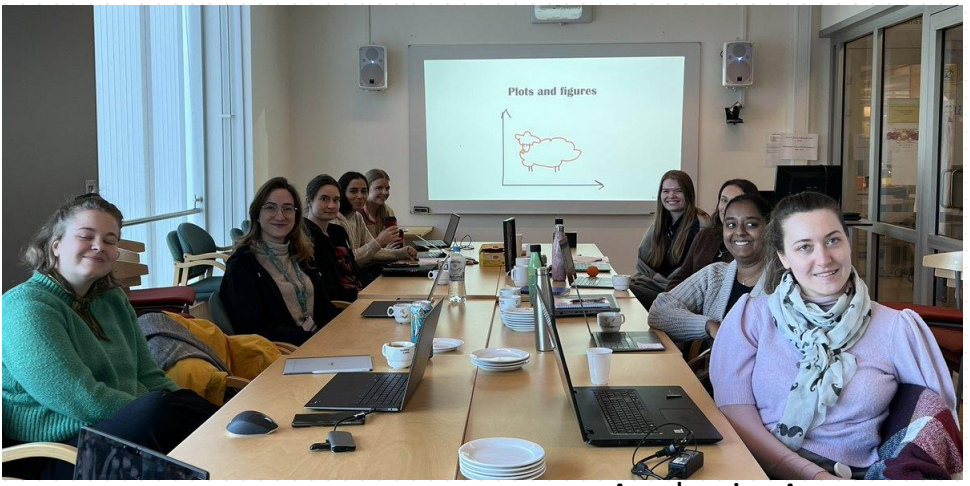
Masteroppgave I farmasi, May 22, 2023

Academics Anonymous

A new intiative started autumn 2022 by Marta Kaminska is academics anonymous. Academics anonymous act as a support group where junior academics (MSc, PhD students, postdocs and researchers) can socialize, networks and learn skills useful for their future careers. Academics anonymous has been hugely popular with BRL members and other junior academics since its inception.

Topics and workshops have included.

Reference managers
Posters
Presentations
Mental health
Abstract writing
Writing papers
Reviewing papers
Rebuttal and publishing process
Constructing project based on an Abstract
Plots and figures
CVs
Finding funding
Work organization



Academics Anonymous

Meetings and Dissemination

What is the value of great research if no one sees it? A core role of members of BRL is the active interaction with the public and wider scientific community. To achieve this, we regularly attend and arrange meetings to present our own work as well as learn from researchers from other institutions.

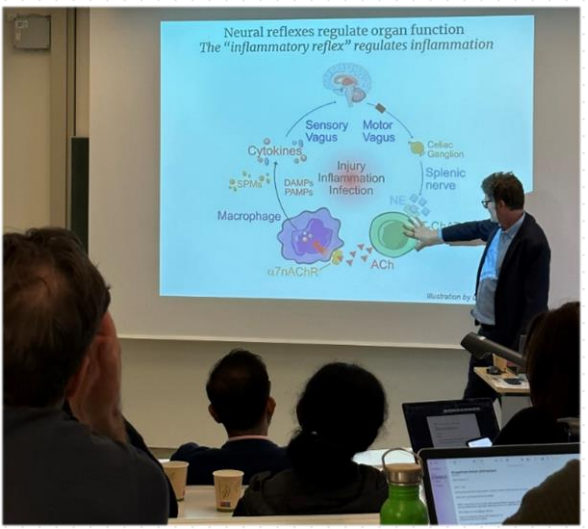
The 24th Broegelmann lecture

The Broegelmann lectures are a series of annually held lectures since 1997 about current hot topics in the field of immunology. The lectures feature nationally and internationally invited speakers and are arranged by the Broegelmann Research Laboratory, NSI Bergen and the Bergen Research School in Inflammation.

The 24th Broegelmann lecturer was **Peder Olofsson**, MD, PhD, Karolinska Institute and Stockholm Centre for Bioelectronic Medicine.

Peder gave a talk titled with "**REACHING BEYOND INNERVATION TO MAP MECHANISMS OF NEURAL REGULATION OF INFLAMMATION"** focused on the field of Bioelectronic medicine, a groundbreaking discipline aimed at interfacing electronics with nerves to specifically target the biological processes underlying disease.

Peder S. Olofsson studies neurophysiological and molecular mechanisms in the neural control of inflammation outside of the central nervous system. His interdisciplinary lab combines molecular medicine, neuroscience, and biomedical engineering, and uses genetic experimental animal models and pharmacological and neurophysiological interventions to map the homeostatic reflex control of inflammation physiology.



BRSI invited speakers

The Bergen Research School in Inflammation arranges lectures from international experts in immunology through HUIMM901 - Project seminars in immunology. Students and researchers are given the opportunity to meet and discuss research with the presenters.

Invited international speakers for HUIMM901 in 2023 were:

Juhi Bagaitkar, PhD, Principal Investigator in the Center for Microbial Pathogenesis and an Associate Professor in the Department of Pediatrics at The Ohio State University.

Juhi is an NIH funded investigator whose research focuses on understanding host-pathogen interactions, and innate immune pathways that regulate tolerogenic immunity at the oral mucosal barrier. Juhi gave a talk titled **"Type III Interferons and oral mucosal antiviral immunity"**.

Riitta Lahesmaa, PhD, Professor of Systems immunology and Director of Turku Bioscience Centre, Turku Finland.

Her research focuses on molecular systems immunology and aims at understanding regulation of immune response and molecular mechanisms of type 1 diabetes and other human immune mediated diseases. Her studies have resulted in the identification of novel molecular mechanisms and new regulators of T cell functions. The lecture was titled **"New regulators of human T-cell differentiation"**.

Articles at a glance

Helena Erlandsson Harris:

A long term goal with my research on the alarmin HMGB1 is to develop treatments that inhibit the inflammatory properties of extracellular HMGB1. One such treatment modality could be the use of a monoclonal antibody neutralising HMGB1. We have studied the effect of one such monoclanal antibody, 2G7, in multiple disease models and even made a humanized version of the original murine antibody. In this study, our collaborators at the University of Munich demonstrated the involvement of HMGB1 in experimental kidney ischemic reperfusion injury and the beneficial effects on long-term outcome by 2G7 treatment.

BASIC RESEARCH www.jasn.org

Tubular Epithelial Cell HMGB1 Promotes AKI-CKD Transition by Sensitizing Cycling Tubular Cells to Oxidative Stress: A Rationale for Targeting HMGB1 during AKI Recovery

Zhi Bo Zhao,[1] Julian A. Marschner,[1] Takamasa Iwakura,[1] Chenyu Li,[1] Manga Motrapu,[1] Meisi Kuang,[1] Bastian Popper,[2] Andreas Linkermann,[3] Jan Klocke,[4] Philipp Enghard,[4] Yoshiharu Muto,[5] Benjamin D. Humphreys,[5,6] Helena Erlandsson Harris,[7] Paola Romagnani,[8] and Hans-Joachim Anders[1]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background Late diagnosis is a hurdle for treatment of AKI, but targeting AKI-CKD transition may improve outcomes. High mobility group box-1 (HMGB1) is a nuclear regulator of transcription and a driver of necroinflammation in AKI. We hypothesized that HMGB1 would also modulate AKI-CKD transition in other ways.

Methods We conducted single-cell transcriptome analysis of human and mouse AKI and mouse *in vivo* and *in vitro* studies with tubular cell-specific depletion of *Hmgb1* and HMGB1 antagonists.

Results HMGB1 was ubiquitously expressed in kidney cells. Preemptive HMGB1 antagonism with glycyrrhizic acid (Gly) and ethyl pyruvate (EP) did not affect postischemic AKI but attenuated AKI-CKD transition in a model of persistent kidney hypoxia. Consistently, tubular *Hmgb1* depletion in Pax8 rtTA, TetO Cre, *Hmgb1*$^{fl/fl}$ mice did not protect from AKI, but from AKI-CKD transition. *In vitro* studies confirmed that absence of HMGB1 or HMGB1 inhibition with Gly and EP does not affect ischemic necrosis of growth-arrested differentiated tubular cells but increased the resilience of cycling tubular cells that survived the acute injury to oxidative stress. This effect persisted when neutralizing extracellular HMGB1 with 2G7. Consistently, late-onset HMGB1 blockade with EP started after the peak of ischemic AKI in mice prevented AKI-CKD transition, even when 2G7 blocked extracellular HMGB1.

Conclusion Treatment of AKI could become feasible when (*1*) focusing on long-term outcomes of AKI; (*2*) targeting AKI-CKD transition with drugs initiated after the AKI peak; and (*3*) targeting with drugs that block HMGB1 in intracellular and extracellular compartments.

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Treatment of AKI has remained challenging when focusing on AKI itself because, in most clinical settings, the diagnosis of AKI implies that kidney injury has already occurred and can no longer be significantly modulated. By contrast, focusing on long-term outcomes of AKI in AKI survivors seems more promising but would require drug interventions that are still efficacious when initiated after the peak of AKI. Survivors of an AKI frequently develop CKD because of an irreversible loss of tubular cells in the acute phase and an ongoing loss of tubular cells thereafter.[1–4] Adaptation of the remaining tubular cells to an increased metabolic demand

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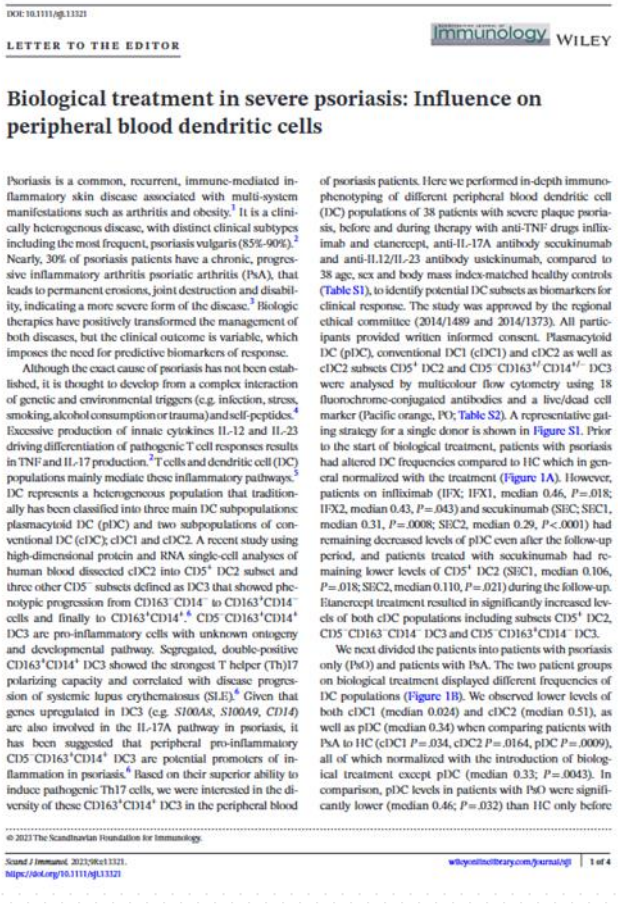
Correspondence: Dr. Hans-Joachim Anders, Medizinische Klinik und Poliklinik IV Klinikum der Universität München Ziemssenstr. 1, D-80336 München, Germany. Email: hjanders@med.uni-muenchen.de

Silke Appel:

Psoriasis is a chronic immune-mediated disease of the skin associated with multi-system manifestations. Up to 30% of patients with psoriasis have psoriatic arthritis (PsA). Biologic therapies have positively transformed the management of both diseases, but the clinical outcome is variable, which imposes the need for predictive biomarkers of response.

In this study we performed in-depth immunophenotyping of different peripheral blood dendritic cell (DC) populations of patients with severe plaque psoriasis, before and during therapy with anti-TNF drugs infliximab and etanercept, anti-IL-17A antibody secukinumab, and anti-IL12/IL-23 antibody ustekinumab to identify potential DC subsets as biomarkers for clinical response. The frequencies of various DC subpopulations differed in patients compared to controls as well as patients with psoriasis compared to psoriatic arthritis, but mostly did not change upon treatment. We observed persistent low levels of peripheral blood plasmacytoid DC in patients with PsA, and in patients with psoriasis treated with infliximab and secukinumab. In addition, secukinumab-treated patients showed sustained low levels of peripheral blood CD5+ DC2. None of the populations correlated to clinical outcomes. The persisting low levels of pDC in peripheral blood in patients with PsA might relate to the presence of arthritis and should be further investigated.



DOI: 10.1111/sji.13321

LETTER TO THE EDITOR

Immunology WILEY

Biological treatment in severe psoriasis: Influence on peripheral blood dendritic cells

Psoriasis is a common, recurrent, immune-mediated inflammatory skin disease associated with multi-system manifestations such as arthritis and obesity.[1] It is a clinically heterogenous disease, with distinct clinical subtypes including the most frequent, psoriasis vulgaris (85%-90%).[2] Nearly, 30% of psoriasis patients have a chronic, progressive inflammatory arthritis psoriatic arthritis (PsA), that leads to permanent erosions, joint destruction and disability, indicating a more severe form of the disease.[3] Biologic therapies have positively transformed the management of both diseases, but the clinical outcome is variable, which imposes the need for predictive biomarkers of response.

Although the exact cause of psoriasis has not been established, it is thought to develop from a complex interaction of genetic and environmental triggers (e.g. infection, stress, smoking, alcohol consumption or trauma) and self-peptides.[4] Excessive production of innate cytokines IL-12 and IL-23 driving differentiation of pathogenic T cell responses results in TNF and IL-17 production.[2] T cells and dendritic cell (DC) populations mainly mediate these inflammatory pathways.[5] DC represents a heterogeneous population that traditionally has been classified into three main DC subpopulations: plasmacytoid DC (pDC) and two subpopulations of conventional DC (cDC); cDC1 and cDC2. A recent study using high-dimensional protein and RNA single-cell analyses of human blood dissected cDC2 into $CD5^+$ DC2 subset and three other $CD5^-$ subsets defined as DC3 that showed phenotypic progression from $CD163^-CD14^-$ to $CD163^+CD14^-$ cells and finally to $CD163^+CD14^+$.[6] $CD5^-CD163^+CD14^+$ DC3 are pro-inflammatory cells with unknown ontogeny and developmental pathway. Segregated, double-positive $CD163^+CD14^+$ DC3 showed the strongest T helper (Th)17 polarizing capacity and correlated with disease progression of systemic lupus erythematosus (SLE).[6] Given that genes upregulated in DC3 (e.g. *S100A8, S100A9, CD14*) are also involved in the IL-17A pathway in psoriasis, it has been suggested that peripheral pro-inflammatory $CD5^-CD163^+CD14^+$ DC3 are potential promoters of inflammation in psoriasis.[6] Based on their superior ability to induce pathogenic Th17 cells, we were interested in the diversity of these $CD163^+CD14^+$ DC3 in the peripheral blood of psoriasis patients. Here we performed in-depth immunophenotyping of different peripheral blood dendritic cell (DC) populations of 38 patients with severe plaque psoriasis, before and during therapy with anti-TNF drugs infliximab and etanercept, anti-IL-17A antibody secukinumab and anti-IL12/IL-23 antibody ustekinumab, compared to 38 age, sex and body mass index-matched healthy controls (Table S1), to identify potential DC subsets as biomarkers for clinical response. The study was approved by the regional ethical committee (2014/1489 and 2014/1373). All participants provided written informed consent. Plasmacytoid DC (pDC), conventional DC1 (cDC1) and cDC2 as well as cDC2 subsets $CD5^+$ DC2 and $CD5^-CD163^{+/-}CD14^{+/-}$ DC3 were analysed by multicolour flow cytometry using 18 fluorochrome-conjugated antibodies and a live/dead cell marker (Pacific orange, PO; Table S2). A representative gating strategy for a single donor is shown in Figure S1. Prior to the start of biological treatment, patients with psoriasis had altered DC frequencies compared to HC which in general normalized with the treatment (Figure 1A). However, patients on infliximab (IFX; IFX1, median 0.46, $P = .018$; IFX2, median 0.43, $P = .043$) and secukinumab (SEC; SEC1, median 0.31, $P = .0008$; SEC2, median 0.29, $P < .0001$) had remaining decreased levels of pDC even after the follow-up period, and patients treated with secukinumab had remaining lower levels of $CD5^+$ DC2 (SEC1, median 0.106, $P = .018$; SEC2, median 0.110, $P = .021$) during the follow-up. Etanercept treatment resulted in significantly increased levels of both cDC populations including subsets $CD5^+$ DC2, $CD5^-CD163^-CD14^-$ DC3 and $CD5^-CD163^+CD14^-$ DC3.

We next divided the patients into patients with psoriasis only (PsO) and patients with PsA. The two patient groups on biological treatment displayed different frequencies of DC populations (Figure 1B). We observed lower levels of both cDC1 (median 0.024) and cDC2 (median 0.51), as well as pDC (median 0.34) when comparing patients with PsA to HC (cDC1 $P = .034$, cDC2 $P = .0164$, pDC $P = .0009$), all of which normalized with the introduction of biological treatment except pDC (median 0.33; $P = .0043$). In comparison, pDC levels in patients with PsO were significantly lower (median 0.46; $P = .032$) than HC only before

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JOURNAL OF Periodontology

ORIGINAL ARTICLE

Bestatin as a treatment modality in experimental periodontitis

Marta Kaminska[1] | **Malgorzata Benedyk-Machaczka**[2] | **Karina Adamowicz**[2] | **Ardita Aliko**[1] | **Kamila Drzazga**[2] | **Klaudia Słysz**[2] | **Ewa Bielecka**[3] | **Jan Potempa**[2,4] | **Piotr Mydel**[1,2]

[1]Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway
[2]Department of Microbiology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Kraków, Poland
[3]Małopolska Biotechnology Centre, Jagiellonian University, Kraków, Poland
[4]Department of Oral Immunology and Infectious Diseases, University of Louisville School of Dentistry, Louisville, Kentucky, USA

Correspondence
Piotr Mydel, Department of Clinical Science, University of Bergen, Jonas Lies vei 87, 5021 Bergen, Norway.
Email: piotr.mydel@uib.no

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Abstract

Background: Chronic periodontitis (CP), the most prevalent dysbiotic bacteria-driven chronic inflammatory disease, is an underestimated global health problem in itself, and due to a causative relationship with other disorders such as cardiovascular diseases or Alzheimer disease. The CP pathogenesis is primarily driven by *Porphyromonas gingivalis* in humans, and *Porphyromonas gulae* in dogs. These microorganisms initiate a pathogenic shift in the composition of the tooth-surface microflora. Our objective was to evaluate antimicrobial effects of bestatin, a potential CP drug candidate.

Methods: We evaluated bestatin bacteriostatic efficiency against periodontopathogens in planktonic cultures via microplate assay, and mono- and multispecies oral biofilm models. Neutrophil bactericidal activities, such as phagocytosis, were investigated in vitro using granulocytes isolated from the peripheral blood. The therapeutic efficacy and the immunomodulatory function of bestatin was assessed in a murine model of CP.

Results: Bestatin exhibited bacteriostatic activity against both *P. gingivalis* and *P. gulae*, and controlled the formation and species composition of the biofilm. We demonstrated that bestatin promotes the phagocytosis of periodontopathogens by neutrophils. Finally, we found that providing bestatin in the animal feed prevented alveolar bone resorption.

Conclusions: We show that in a murine model of CP bestatin not only shifted the biofilm species composition from pathogenic to a commensal one, but also promoted bacteria clearance by immune cells and alleviated inflammation. Taken together, these results suggest that bestatin is a promising drug choice for the treatment and/or prevention of periodontitis and clinical trials are required to fully evaluate its potency.

KEYWORDS
bestatin, biofilm, periodontitis, *Porphyromonas gingivalis*, *Porphyromonas gulae*

Piotr Mydel:

One of our research aims is to address the global health problem of chronic periodontitis (CP) and identify novel drug candidates. In this study, we evaluated the antimicrobial effects of bestatin and demonstrated its bacteriostatic activity against key periodontopathogens such as P. gingivalis and P. gulae. Bestatin effectively controlled biofilm formation and composition. Additionally, bestatin enhanced the phagocytic activity of neutrophils, promoting the clearance of these pathogens both in vitro and in vivo. These findings suggest that bestatin could be a promising therapeutic option for the treatment and prevention of periodontitis, warranting further clinical trials to evaluate its efficacy.

BRL meeting representation

BRL was represented at a number of local, national and international meetings in 2023. Meetings attended by BRL researchers and students included

41st Annual Meeting and General Assembly of the Norwegian Society for Immunology (NSI), Oslo, Norway

Annual European Congress of Rheumatology, Milan, Italy

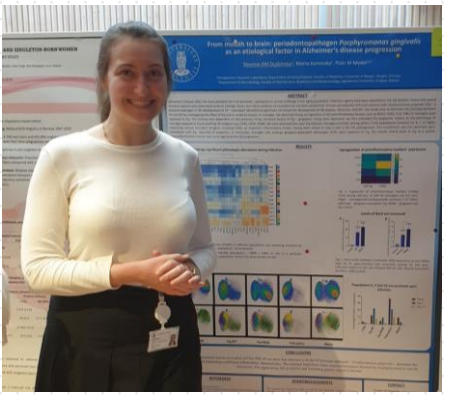
49th Annual Meeting Scandinavian Society of Immunology, Turku, Finland

Cyto 2023, The Congress for the International Society for the Advancement of Cytometry, Montréal, Québec, Canada

NeuroGASTRO 2023, Meeting of the European Society of Neurogastroenterology and Motility, Bucharest, Romania

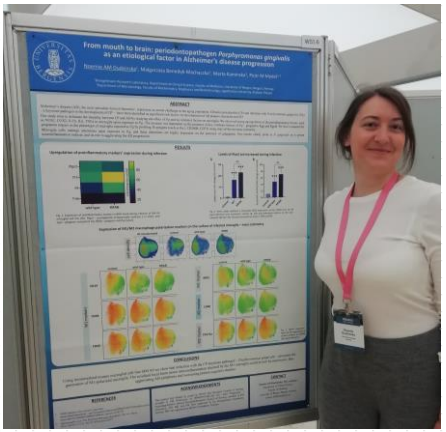
UiB Research School in Clinical Medicine, 17th Annual Research Presentations. Marta Kaminska won the open class and people's choice award winner for "Bestatin as a promising periodontitis drug candidate".

Valéria Valim, Universidade Federal do Espírito Santo, Brazil, visits Sjögren's group

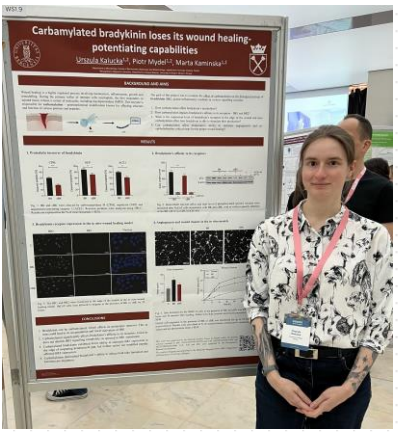


Noemie, Research day at Faculty of Medicine, UiB

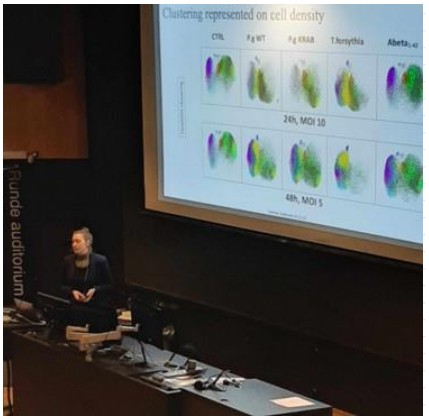
Combined Karolinska Institutet and BRL HMGB1 group meeting.



Noemie, SSI meeting



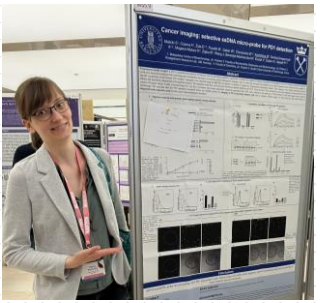
Ula, SSI meeting



Noemie, NSI meeting

Piotr & Marta, IUIS

Marta, Silke and Roland, SSI meeting



Marta, SSI meeting

Financial support

Knowledge creation and dissemination are fueled by a crucial resource: research funding and grants. BRL thanks the organizations, institutions and foundations that enable us to carry out our research.

The Broegelmann Foundation
(Kjøbmand J.P. Broegelmanns Legat)

The Broegelmann Research Laboratory was inaugurated in 1957, made possible by the legacy of merchant Johan Henrik Broegelmann.
JH Brogelmann had inherited a successful fabrics and finer ladies' clothing business from his father, Johan Petter Broegelmann. In his will, JH Broegelmann expressed his wish that his assets should form the basis for a foundation that in the name of his father should support humanitarian projects. He appointed his long-term co-worker Ingeborg Berg Nielsen as executer of his will. Ingeborg Berg Nielsen established the Merchant JP Broegelmann foundation with the purpose of supporting research on unexplored diseases performed at the University of Bergen; for example, rheumatism, polio or cancer. Ingeborg Berg Nielsen further bequeathed her own assets to the foundation.
Thus, in 1957 the Broegelmann Research Laboratory could be inaugurated and has since then contributed the research field of immunology, including rheumatic diseases such as arthritis and Sjögren's syndrome. Even today, 65 years later, the support of the foundation with the fund managed by the The Broegelmann Research Board (see below), forms the basis for immunology research at the University of Bergen.

Attorney at Law
Bernt Jacob Pettersen
Chairman

Professor, MD, PhD
Lars A. Akslen

Professor, MD, PhD
Robert Bjerknes

Major grants 2023

2019 – 2024
Piotr Mydel: National Institutes of Health (RO1 DE022597) “Bacterial peptidylarginine deiminase, a link between gums and joint disease”, Total 6.4 mill NOK

2020 – 2023
Foundation for Research in Rheumatology (FOREUM) “Genetic variants associated with Sjögren’s syndrome leading to differential gene expression in males and females and their functional impact on the immune system”; Karolinska Institutet v/Marie Wahren Herlenius er coordinator, UiB og Harvard er partnere. Appel/Jonsson Total 1.5 mill NOK

2020 – 2024
Piotr Mydel: EU Joint Programme – Neurodegenerative Disease Research (EC/JPND; ES655895) “Alzheimer’s disease as a co-morbidity of chronic periodontitis with *Porphyromonas gingivalis* as a causative link between both diseases” Total 575 000 €

2019 – 2024
Roland Jonsson: The European Commission Horizon 2020 contract NECESSITY (IMI2-JU/EU/H2020 nr. 806975) “New Clinical Endpoints in primary Sjögren’s Syndrome: an Interventional Trial based on stratifying patients”

2021 – 2024
Piotr Mydel: EC/Grieg “Novel mechanisms of PAD activity regulation. Substrate specificity and activation of peptidyl arginine deiminases in the context of RA” Total 499 000 €

2021 – 2025
Yenan Bryceson: Norwegian Research Council ‘’Engineering NK cells for improved functionality in immunotherapy’’ Total 12 mill NOK

2021 – 2025
Marie Wahren Herlenius: Norwegian Research Council ‘’The molecular basis of sex differences in Sjögren’s syndrome’’ Total 10 mill NOK

2022 – 2023
Helena Erlandsson Harris: Norwegian Rheumatism Association ‘’ Molecular profiling of juvenile idiopathic arthritis, a necessary basis for implementation of precision medicine’’ Total 300 000 NOK

2023 – 2027
Piotr Mydel: National Science Center Poland (2022/47/B/NZ4/01696) “Impact of uremic carbamylation on RAA system and endothelial dysfunction”; Total 6 mill NOK

2023 – 2027
Marta Kaminska: Nasjonalforeningen for folkehelse “Vascular damage: exploring the link between chronic periodontitis and Alzhiemer’s disease ”; Total 3 mill NOK

We are greatful for the financial support to our research projects

Forskningsrådet
The Research Council of Norway

EU

NRF Norsk Revmatikerforbund

FOREUM
Foundation for Research in Rheumatology

National Science Centre Poland

Nasjonalforeningen for folkehelsen

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Broegelmann Research Laboratory
Department of Clinical Science / University of Bergen
The Laboratory Building, 5th floor / Haukeland University Hospital Jonas
Lies vei 87 / N-5021 Bergen, Norway post@uib.no / 55 58 00 00

uib.no/rg/broegelmann