Annual Activity Report 2024

LEO Foundation
Skin Immunology
Research Center

Content

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Introduction

The LEO Foundation Skin Immunology Research Center (SIC) has a unique 10-year perspective to advance research and education of inflammatory skin diseases.

The skin is our largest barrier to the external environment and the number of skin diseases exceeds 3,000. In Denmark, skin diseases remain one of the most common reasons to seek medical consultation and up to 20% of school children suffer from atopic dermatitis. Knowledge of disease mechanisms has accelerated over the past decade and discoveries within immunology have paved the way for new treatments. Despite this significant progress, curative treatments for common inflammatory skin diseases are not yet available, and these diseases come with a large impact on quality of life as well as on society as a whole. Co-morbidities in other barrier tissues are common and with rapid development of immunomodulatory treatments for psoriasis and atopic dermatitis, it is increasingly clear that dampening inflammation in the skin may lead to inflammation in other parts of the body.

The LEO Foundation Skin Immunology Research Center (SIC) was established to advance research and education in common inflammatory skin diseases at the University of Copenhagen in 2019, based on an ambitious donation of DKK 400 million over 10 years by the LEO Foundation. SIC focuses on the common inflammatory skin diseases psoriasis, atopic and contact dermatitis but we also cover cutaneous T cell lymphoma as a model disease of T cell driven pathology in skin. SIC aims to bridge and integrate basic and clinical analysis of the skin to advance our understanding and treatment of skin diseases. With new recruitments, SIC has secured interdisciplinary excellence from mucosal barriers to address the increasingly appreciated co-morbidities that occur in common inflammatory skin diseases. Our research covers many different perspectives of fundamental research with impact on patients living with inflammatory skin diseases.

Importantly, we educate scientists with the aim of nurturing the next generation of leaders in the field, concurrently increasing the knowledge and awareness of skin diseases among medical professionals, patients, and the public. We aim to become an international leader in skin research and a beacon for skin health and research in Denmark.

MISSION

To better understand, prevent and treat skin diseases for the benefit of the individual patient.

VISION

- Lead discoveries of mechanisms that cause and maintain skin diseases
- Be an international center of excellence for barrier tissue immunology research
- Educate the next generation of research leaders in barrier tissue immunology

KEY RESEARCH THEMES

- Skin disease mechanisms
- Patient stratification and precision medicine
- Novel ways to attack and cure skin diseases

Director's Corner

Executive Director of SIC, Professor Niels Ødum.

Breaking Barriers in Skin Immunology: Advancing Research and Global Collaborations.

The skin serves as a crucial barrier against the external environment, helping to maintain a healthy body. Enabled by the LEO Foundation's generous donation in 2019, the LEO Foundation Skin Immunology Research Center (SIC) has established itself as an internationally leading center in skin immunology. While maintaining a strong foundation in immune-skin interactions, we are now strategically expanding our research to explore how skin biology is interconnected with processes and diseases in other organs and tissues.

Reflecting on 2024, I am proud to highlight a year of major scientific advancements, strengthened collaborations, and strategic growth. Our research has led to significant discoveries in inflammation, immune regulation, and skin diseases with publications in high impact journals. Key breakthroughs include uncovering the role of $CD8^+$ epidermal-resident memory T cells in prolonged skin barrier dysfunction as well as identifying a novel mechanism regulating tissue sensitivity to TNF-driven inflammation with implications for chronic diseases such as psoriasis. Additionally, studies on atopic dermatitis revealed unexpected anti-inflammatory mechanisms, potentially influencing future allergy and eczema treatments. In cancer biology, SIC researchers identified genetically distinct subclones in T cell skin lymphoma with differential treatment responses and demonstrated that *Staphylococcus aureus* drives cancer drug resistance, opening avenues for novel therapeutic strategies. Research on mesenchymal stem cells (MSC) identified key factors influencing their immunomodulatory properties and optimised methods for their in vitro expansion while preserving functionality. Through advanced sequencing technologies, specimens from patients, and transgenic models, SIC continues to investigate basic immunology, disease-associated type 2 immune responses, tumor immunology, and immune-fibroblast interactions, contributing to international initiatives such as the Gut Cell Atlas, with major studies set for publication in 2025.

Our research infrastructure has been dramatically advanced with the establishment of a wildling rodent facility – one of only

four worldwide – to investigate microbiota-driven disease mechanisms. Recognising the impact of skin colour on disease presentation and pathology, we have initiated long-term collaborations with expert dermatology-centers in Sub-Saharan Africa, facilitating researcher exchange and capacity-building for a strong international research network.

A major milestone this year was the recruitment of a leading research group in immunological bioinformatics, headed by Professor Lars Rønn Olsen, bringing cutting-edge computational approaches and expertise to SIC. Additionally, two research teams, led by early-career scientists awarded the prestigious Dr. Abildgaard Research Grant, are ensuring a continued infusion of innovative perspectives. We have also welcomed new Bridge Fellows, fostering interdisciplinary collaborations across diverse research fields. Furthermore, our rapidly growing collaboration with the BIOSKIN program is strengthening our translational and clinical research, bridging the gap between fundamental discoveries and real-world applications.

Hosting visiting scientists – including master's and PhD students, clinicians, and professors from the USA, UK, EU, and Africa – has enriched our research environment and strengthened international partnerships. Likewise, SIC researchers have benefited from research stays at leading institutions such as Stanford University, the University of California, Irvine, and the Swiss Institute of Allergy and Asthma Research (SIAF), some of which have already resulted in a *Science* publication, with further manuscripts in progress.

As detailed in other parts of this report, our commitment to education spans from high school outreach, university courses, PhD training, to our renowned international summer school, which brings together young researchers and experts worldwide. Our young investigator network continues to thrive, and we actively engage in scientific outreach through conference participation, EMBO workshops, and the organisation of international meetings, including the upcoming European Society of Contact Dermatitis Congress in 2026. Likewise, the SIC community actively participates in public outreach through news articles, seminars, podcasts, and social media.

Looking ahead, we aim to expand our research frontiers by exploring the interplay between the skin and other barrier organs (e.g., lung, gut, blood-brain barrier), broadening our thematic and geographic focus (Sub-Saharan Africa), and enhancing our bioinformatics and technological capabilities through cutting-edge spatial transcriptomics, a wildling rodent facility, and novel skin models. Entering 2025, SIC is poised to drive further scientific innovation and translational breakthroughs, advancing novel treatments for inflammatory and immune-related diseases.

With great anticipation for the opportunities ahead, I extend my deepest gratitude to the LEO Foundation for their continued support, which makes our work possible.

Reflections from the Dean

Bente Merete Stallknecht is Dean of the Faculty of Health and Medical Sciences, University of Copenhagen.

From my perspective, 2024 has been a truly remarkable year for the LEO Foundation Skin Immunology Research Center (SIC), marked by significant conceptual, experimental, and strategic advancements in key areas of importance to both SIC and the University.

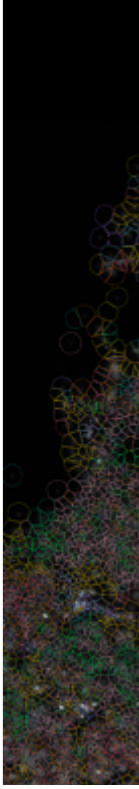
I am particularly encouraged by SIC's pioneering initiatives in Africa. With projects underway in Tanzania and South Africa, SIC is forging new partnerships with local institutions while drawing on the long-standing collaborations established by ISIM. Although still in their early stages, these projects are rapidly gaining momentum, underscoring their potential as a highly promising and productive avenue for scientific and educational collaboration. Their success has further reinforced SIC's and the University's commitment to expanding our engagement with African partners in the coming years.

Looking ahead, the planned opening of the wildling facility represents a milestone development for both SIC and the University. As one of only a handful of such facilities worldwide, it will provide an unparalleled setting for investigating microbiota-driven disease mechanisms and other pressing biomedical questions, ultimately deepening our understanding of complex biological processes.

Recognising that strong expertise in bioinformatics is fundamental to health science research, I am pleased to see the center taking steps to reinforce this field with the appointment of Professor Lars Rønn Olsen, a distinguished, internationally recognised specialist in immunological bioinformatics, who will establish an independent research group. The appointment of Professor Lars Rønn Olsen will mark an exciting new chapter for SIC and further strengthen its research profile.

I am also delighted by the outstanding achievements of our early-career researchers, whose talent and dedication have been recognised through numerous prestigious awards. Their success, including honours such as the Dr Abildgaard recognitions, reflects the exceptional potential within the SIC community and bodes well for the future.

Finally, it is wonderful to see the spirit of enthusiasm, collaboration, and intellectual curiosity that thrives at SIC. The strong sense of community fostered here not only enriches SIC's ongoing research endeavours but also lays a solid foundation for inspiring and nurturing the next generation of scientists.



Professor Lars Rønn Olsen is new Group Leader at SIC.

New Group Leader

Advancing Immunology Through Computational Innovation

Immunology research is producing increasingly complex datasets, making computational expertise essential for extracting meaningful insights. Recognising this need, SIC has significantly strengthened its research profile by welcoming Professor Lars Rønn Olsen, an expert in bioinformatics, along with his team of seven bioinformatics researchers. With over a decade of experience developing and applying algorithms for immunological data analysis, his group brings cutting-edge expertise to SIC.

The group's ongoing close collaboration with immunologists at the University of Copenhagen will now be enhanced by their physical presence at SIC, streamlining the iterative process of single-cell data analysis.

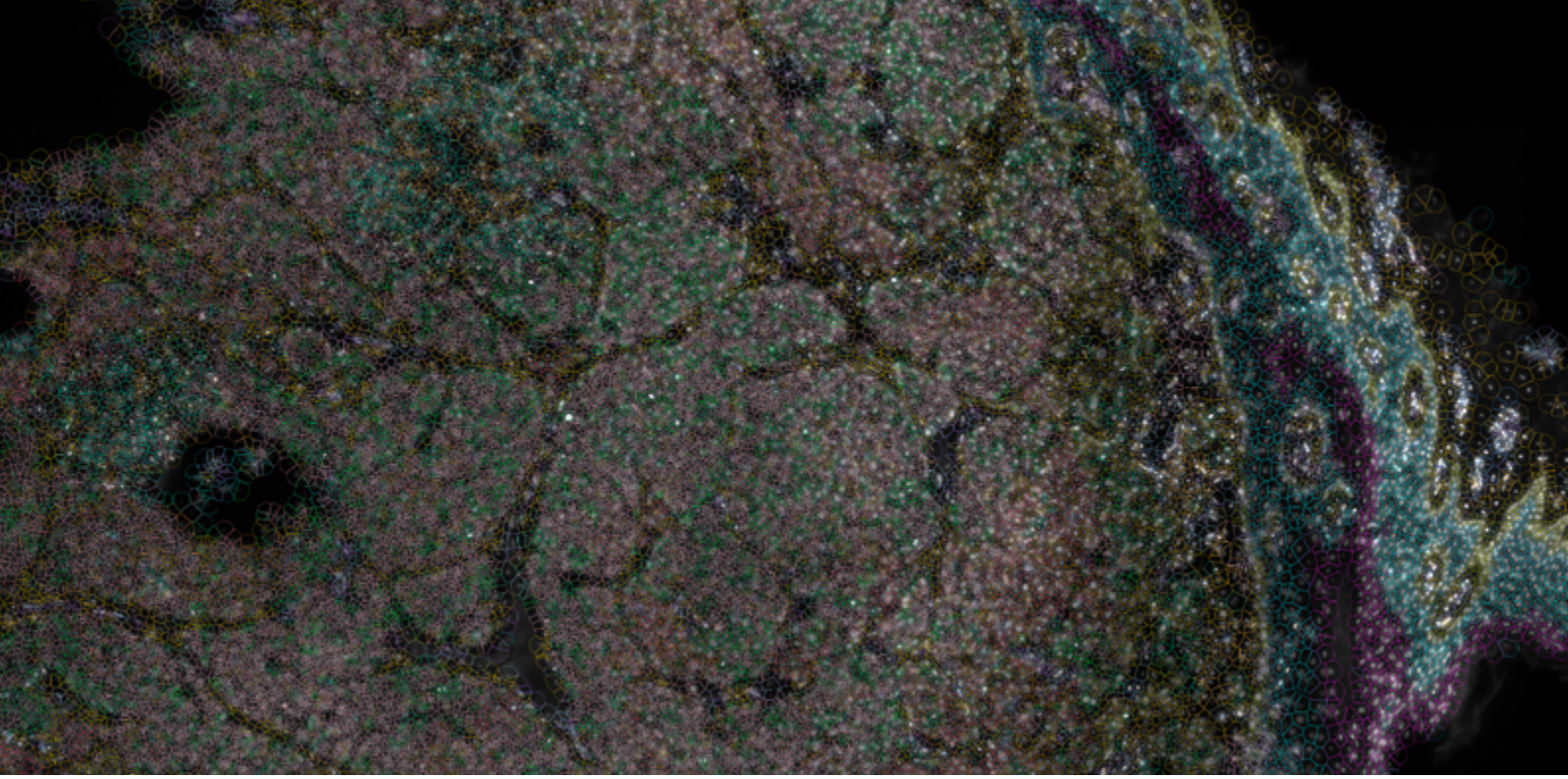
Unlocking the Power of Spatial Transcriptomics

A key new research focus at SIC is the emerging field of spatial transcriptomics, which extends traditional single-cell analysis by enabling the analysis of gene expression patterns in a spatial context. This technology not only allows researchers to understand which cells are present, but also where they are located in the tissue and how their spatial arrangement influences biological function.

"In skin research, spatial context is crucial," Lars explains. "The skin is compartmentalised into specialised structures, and understanding the distribution of cells and their interactions in situ provides deeper insights into disease mechanisms."

While spatial transcriptomics is resource-intensive, Lars emphasises that it is not a luxury but a necessity for addressing fundamental biological questions. "Moving from suspension single-cell analysis to spatial transcriptomics isn't just an incremental improvement – it fundamentally transforms our ability to extract new knowledge."

By combining strong bioinformatics expertise with cutting-edge spatial transcriptomics,



Colour-coded cell segments from human skin, highlighting the high-resolution tissue architecture revealed by spatial transcriptomics using the Xenium *in situ* platform.

SIC is positioning itself at the forefront of immunological discovery. The integration of bioinformatics at every stage of research ensures that SIC remains a leader in extracting meaningful insights from complex biological data.

Strengthening Research Infrastructure and Expertise

SIC is leveraging state-of-the-art spatial transcriptomics platforms available at nearby institutes, ensuring access to cutting-edge technology. However, Lars highlights that instrument choice is only part of the equation. "A critical, often-overlooked factor is the availability of robust analysis pipelines for processing data from specific machines," he notes. "Investing in the wrong platform can lead to hidden costs if extensive software development is required for data analysis."

The team's move to SIC also reflects the center's growing ability to attract top-tier talent in a highly competitive field. "Bioinformatics experts are in high demand, yet our recent PhD opening received nearly 200 applications, including many graduates from elite institutions," he says. "This speaks to SIC's strong research environment and the global significance of our work in immunology."

"We integrate computational considerations from the earliest stages of research projects. This ensures that data acquisition strategies are optimised to maximise the knowledge output, while ensuring efficient downstream analyses and minimising costs."

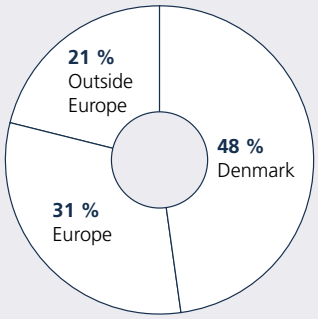
Lars Rønn Olsen

Organisation and governance

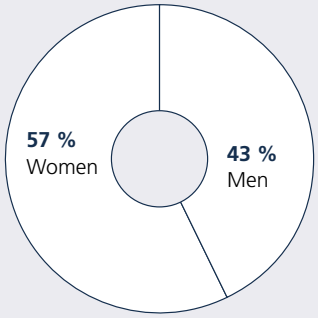
SIC operates as a center within the Department of Immunology and Microbiology (ISIM) at the Faculty of Health and Medical Sciences (SUND) at the University of Copenhagen. Situated at the Mærsk Tower in Copenhagen, SIC's research groups engage in scientific collaborations across the Faculty, national and international clinical research units, and the life science industry.

Staff composition

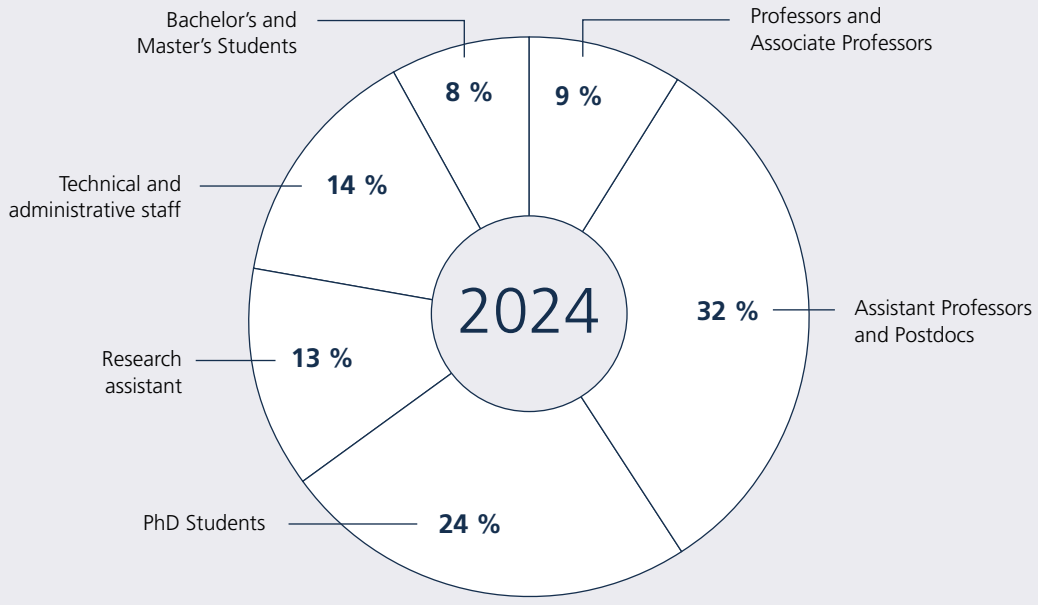
As of the end of 2024, the SIC community consisted of 95 members, representing 24 nationalities. The SIC community includes members of core research groups at SIC (72) and Herlev/Gentofte Hospital (26), visiting researchers, bachelor's and master's students conducting their thesis work or participating in exchange programmes.



Nationalities of scientific staff and students



Gender distribution of scientific staff and students



Distribution of staff and students by position

The core members

SIC hosts seven core groups and affiliated Clinical Professors at Herlev and Gentofte Hospital, Jeanne Duus Johansen and Lone Skov head BIOSKIN. The core members form SIC's Steering Committee, spearheading strategic scientific initiatives and embodying the 'Team Science Concept.'

Management

SIC's Daily Leadership Team, consisting of Executive Director Niels Ødum, ISIM Head of Department Charlotte Menné Bonefeld, Department Administrator Nils Erik Samdal, and Center Coordinator Hannah Paludan, oversees day-to-day operations.

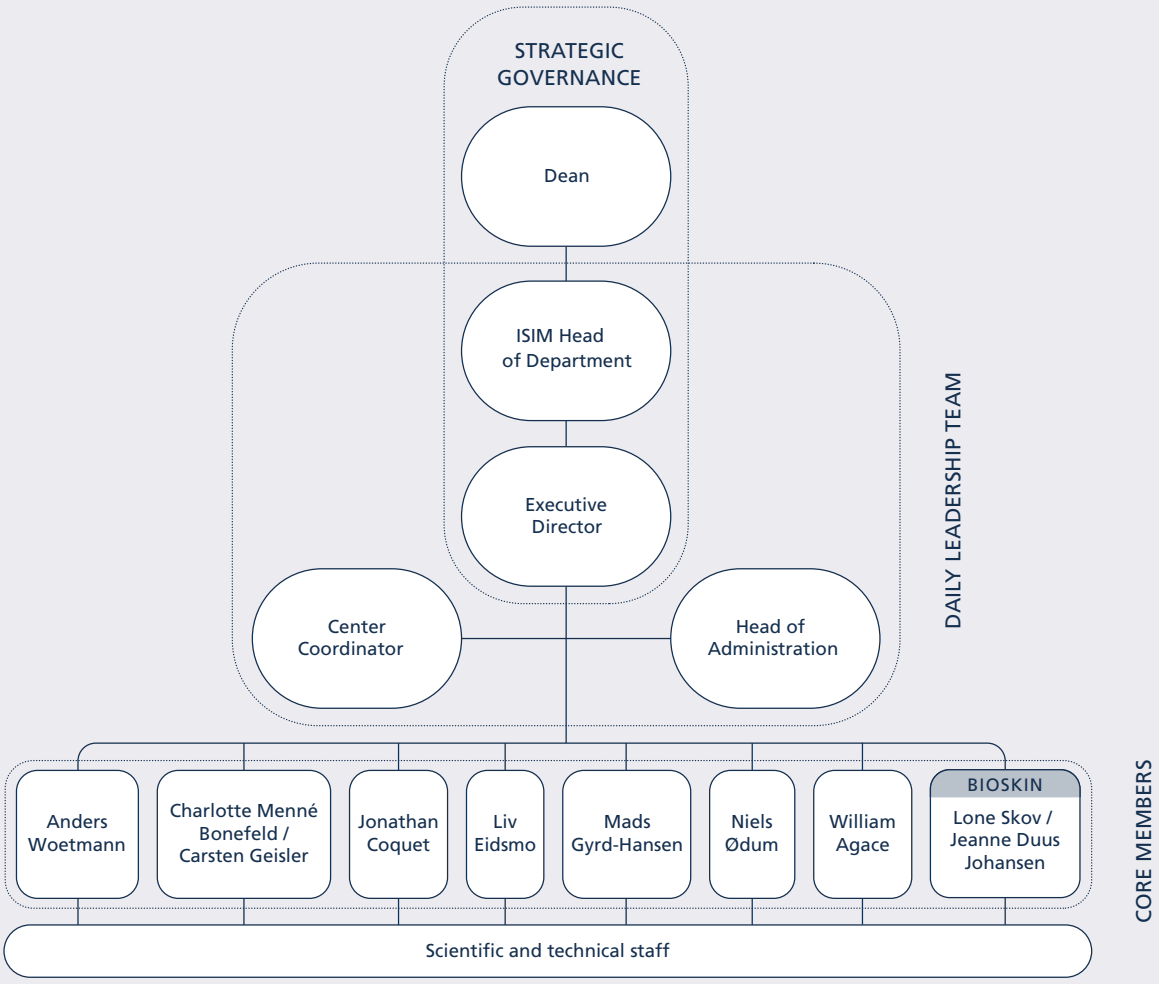
Regular consultations with Dean Bente Merete Stallknecht guide strategic decisions. Annually, Rector Henrik C. Wegener aligns with Center Management and the LEO Foundation to review strategic progress and development. The Center Management also meets annually with the LEO Foundation to present the current strategy and agenda.

Scientific advisory board 2024

The Scientific Advisory Board (SAB) provides guidance on scientific and strategic directions that support the center's international impact.

THE SCIENTIFIC ADVISORY BOARD CONSISTS OF

- Tomas Mustelin, University of Washington, USA (Chair)
- Emmanuella Guenova, University of Lausanne, Switzerland
- Johann Gudjonsson, University of Michigan, USA
- Kenji Kabashima, Kyoto University, Japan
- Mübeccel Akdis, University of Zurich, Switzerland
- Olle Kämpe, Karolinska Institutet, Sweden
- Riitta Lahesmaa, University of Turku, Finland



Organisation and governance chart

Allergic Inflammation

The Allergic Inflammation Group is interested in understanding how our adaptive immune cells, commonly called T and B cells, see, and respond to allergens from our environment. The group focuses on uncovering the nature of the antigens that drive acute and chronic allergic inflammation in different organs including the lungs and the skin, and moreover, to better understand how immune responses evolve to become pathogenic. The group is headed by Associate Professor Jonathan Coquet.

Over the past year, the Allergic Inflammation group has undergone a rapid expansion, bringing in several talented group members. Isabel Ulmert, PhD immunologist, started a postdoctoral research position in February. Thereafter, Jebunnahar Mishu joined our group as a computational biologist and Mattia Dervasi started as a research assistant after the completion of his Masters project in the department. Late in the year, we had the good news that Alma Lindell had been accepted into the PhD programme at the university, and that we would be joined by another immunologist, Kilian Maire, for his postdoctoral research from the beginning for 2025. Last, but not least, we learned during the year that Dr. Wenning Zheng had been awarded the Dr. Abildgaard fellowship from the LEO Foundation and would start as Assistant Professor, affiliated to our group from the beginning of 2025.

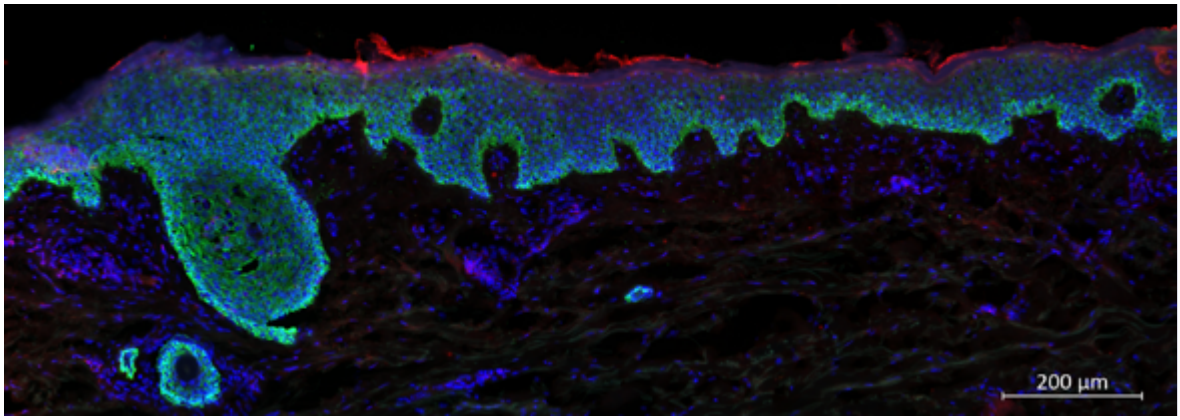
The group had a productive year, collaborating in studies of human barrier type 2 innate lymphocyte biology and intestinal type 2 T cell responses in rhesus macaques. A review of type 2 lymphocyte metabolism was also published at the journal *Current Opinion in Immunology* in addition with collaborative works with the group of Niels Odum and other international collaborators. The group was well represented at meetings around the world with Egon Urgard presenting his work in the 'Rising Star' session at International Congress of Mucosal Immunology in July and Jonathan Coquet invited to teach at

the ENII Sardinia Summer School and speak at the American Academy of Allergy, Asthma and Immunology Meeting in Washington DC, among numerous other presentations.

An ongoing collaboration with Lone Skov at Gentofte hospital saw Alma Lindell work together with Anne-Sophie Henrichsen to analyse the immune composition of the skin in around 50 individuals with atopic dermatitis and in healthy donors. This precious material was analysed by multiparameter flow cytometry and will be supplemented by an analysis of blood from the very same people. Experiments using spatial RNA-Sequencing will help us to precisely locate specific cell types in patients with atopic dermatitis to identify important points of contact. In addition, Javiera Alvarez has conducted an in-depth analysis of a rare malignancy that develops in the nasal sinus barrier called 'sinonasal' cancer. Javiera's analysis, which includes spatial RNA-Sequencing, depicts prominent immunological features of these cancers, with interesting features of adaptive lymphocytes that could have important implications for treatment. Our expectation is that both of these studies will be submitted for publication in 2025.

Moreover, the group established preclinical research models of infection and allergy in which we study the type 2 immune response, which lays a strong foundation for the year ahead. The establishment of a wildling rodent facility in early 2025, which has been approved after lengthy discussions, will provide an invaluable resource for the SIC research family and the broader research community at the university. Wildlings and other microbially-enriched mouse models are becoming the state-of-the-art for preclinical research models and present us with a way to test the influence of microbes on diseases including atopic dermatitis, psoriasis, intestinal inflammatory diseases and many other conditions. This wildling facility will represent only the fourth such known facility in the world.

Thus, the Allergic Inflammation group enters 2025 with a greatly strengthened capacity and a wider range of competencies with which to tackle the conundrum of inflammatory skin and barrier diseases.



Cross-section of the skin of a patient with atopic dermatitis, with noticeable epidermal thickening.

Barrier Immunology

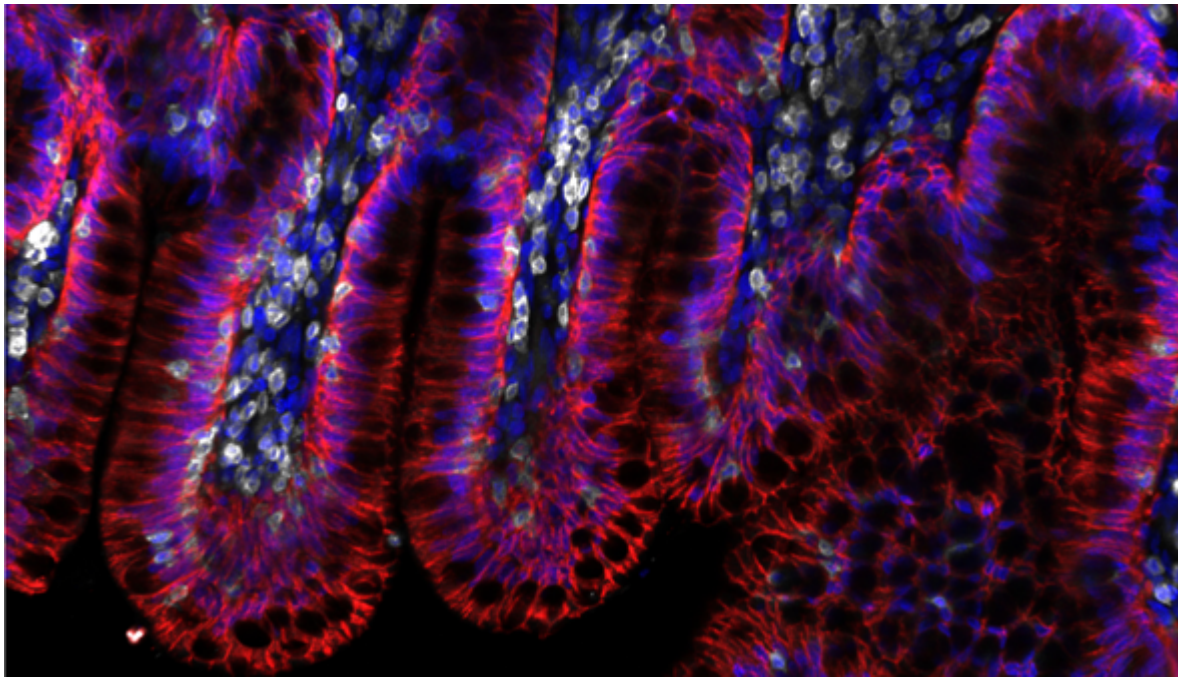
The barrier immunology group at SIC focuses on understanding immune responses at our barrier surfaces and how such responses are altered in disease and contribute to chronic inflammation. We are particularly interested in characterising and understanding; (1) the function of the various immune niches within and along the length of the human intestine; (2) the complex dialogue between the environment, immune cells and tissue resident fibroblasts that help maintain intestinal homeostasis; (3) the alterations in this cross-talk that contribute to the initiation and maintenance of inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis; (4) how immune responses in the intestine may influence diseases of other barrier surfaces such as the skin. The group is headed by William Agace.

Since its initiation in November 2023 the group has expanded dramatically, currently consisting of six postdoctoral fellows, five PhD students and 2 master's students from 9 different nationalities! Approximately half of the group uses state-of-the-art technologies in for example scRNA-seq, scTCR-seq, CITE-seq and spatial transcriptomics to analyse immune compartments and immunological processes active in healthy and diseased human tissues. While the primary focus is the intestine, the group is expanding its activities to assessing comorbidities of the liver and skin. As part of this work, we are heavily involved in international cell atlas initiatives including the Gut Cell Atlas consortium run through the Helmsley Trust, USA. The other half of the group uses a wide range of transgenic mice and immune models to perform in vivo mechanistic studies focusing on understanding the role of fibroblasts as environmental sensors and regulators of immune mediated intestinal homeostasis and disease. Two projects, the first characterising the fibroblast landscape of human gut associated lymphoid tissues in health and IBD, and the second charactering mononuclear phagocyte diversity in the human intestine in health and Crohn's disease, are close

to completion and due to be submitted for publication in the first half of 2025.

During 2024 the group had the pleasure of hosting several visiting scientists including Prof. Stephen McSorley (UC Davis, USA) on a 2-month sabbatical and Prof. Allan Mowat (Glasgow University,) a long-term collaborator and friend of the lab who visited on three separate occasions and used his encyclopaedic knowledge of immunology to give highly appreciated tutorials to SIC members throughout the year. We also had visits from 2 PhD students, Madeline Mellette (Calgary University) and Elisa Melon, (Barcelona University) who stayed 2 and 3 months respectively as well as Dr Gareth Jones (University of Edinburgh) for a shorter 3-day visit. Finally, two of our PhD students Venla Väänänen and Fredrik Junghus spent 3-4 months working in the laboratory of Prof. Eugene Butcher (Stanford University, US).

A highlight of the year for the group was the International Congress of Mucosal Immunology (ICMI), hosted by William Agace and his co organisers Dr Lahl (University of Calgary) and Dr Willinger (Karolinska Institute) at the Tivoli Congress Center, Copenhagen. The ICMI is the premier biannual conference organised by the Society of Mucosal immunology and in 2024 attracted around 700 delegates from around the world for a 1-day preconference school and 3.5-day conference. Members of the group were well represented with 4 short talks and 4 posters, with PhD student Christian Ashworth winning a poster prize. A final shout out to our very own Erik van Tilburg Bernardes who applied for and was awarded two internationally highly competitive postdoctoral fellowship grants (Marie Curie and EMBO) to continue his work within the laboratory! We look forward to continued scientific success and fun in 2025!



The intestine is not only important for nutrient and water absorption but also contains the highest number of immune cells of any organ in the human body. For example, effector T cells (white, CD3) patrol the intestinal mucosa and are in close proximity to the epithelial layer (red, EPCAM), which forms the outermost barrier of the gut. All nucleated cells are shown in blue (DAPI).

Immune Regulation

The Immune Regulation Group at SIC focuses on understanding the regulatory mechanisms that control immune responses in barrier tissues, including the skin, gut, and lungs. Our research explores how immune homeostasis is maintained and what triggers immune dysregulation in inflammatory skin diseases. Additionally, we investigate the influence of microbiota and their metabolites on immune function, with the ultimate aim of developing novel therapeutic strategies. The group is headed by Professor Anders Woetmann and currently comprises four PhD students.

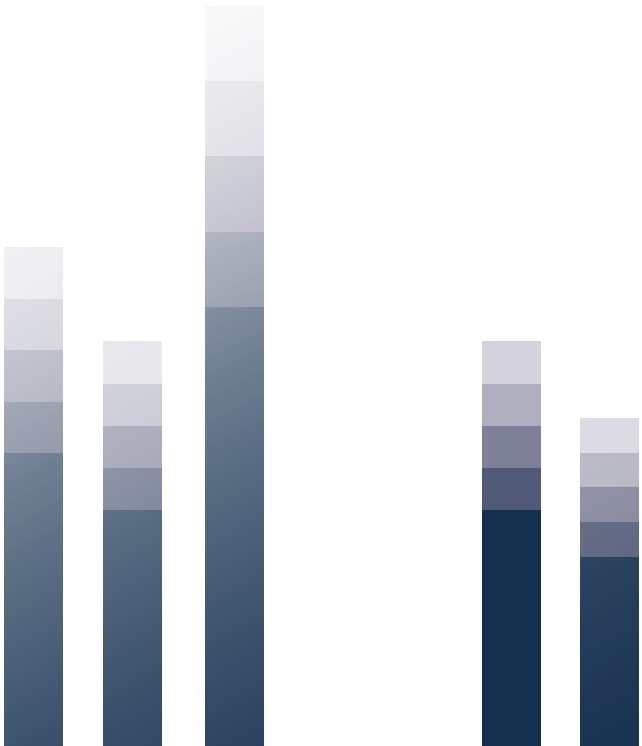
In 2024, we published a review in Frontiers in Medicine on the therapeutic potential of adipose-derived mesenchymal stem cells (AD-MSCs) for inflammatory skin diseases. AD-MSCs are widely studied for their immunomodulatory and regenerative properties, yet their clinical application remains limited due to challenges in efficacy. PhD student Marina Galera Ramirez has been leading efforts to optimise MSC expansion techniques. By comparing 2D and 3D culture systems, as well as small- and large-scale bioreactor platforms, we identified significant differences in gene and protein expression, highlighting the importance of culture conditions in maintaining MSC functionality. One manuscript detailing these findings is currently under revision, while a second manuscript, further examining translational challenges in MSC-based therapies, has been finalised.

Another major research focus is the role of microbiota in modulating immune responses. PhD student Lisa Harth has been investigating the interaction between microbiota and antiviral immune responses in the skin, with several important breakthroughs achieved in 2024. Her findings are expected to contribute to a high-impact publication in 2025.
Our group has also expanded into tumour immunology through a collaboration with the Department of Neurosurgery at Copenhagen University Hospital-Rigshospitalet. PhD student Gillian Dao has applied methods developed

at SIC for analysing immune cell composition of skin to study immune cell infiltration in meningiomas. This collaboration resulted in a 2024 publication in Cancers, with additional manuscripts currently in preparation. Using a newly optimised tumour digestion protocol, we successfully generated single-cell suspensions from meningioma tissues, facilitating in-depth analysis of tumour-infiltrating immune cells. Our results revealed a predominance of antigen-presenting cells with immunosuppressive phenotypes, along with T cells and macrophages, which may serve as future therapeutic targets.

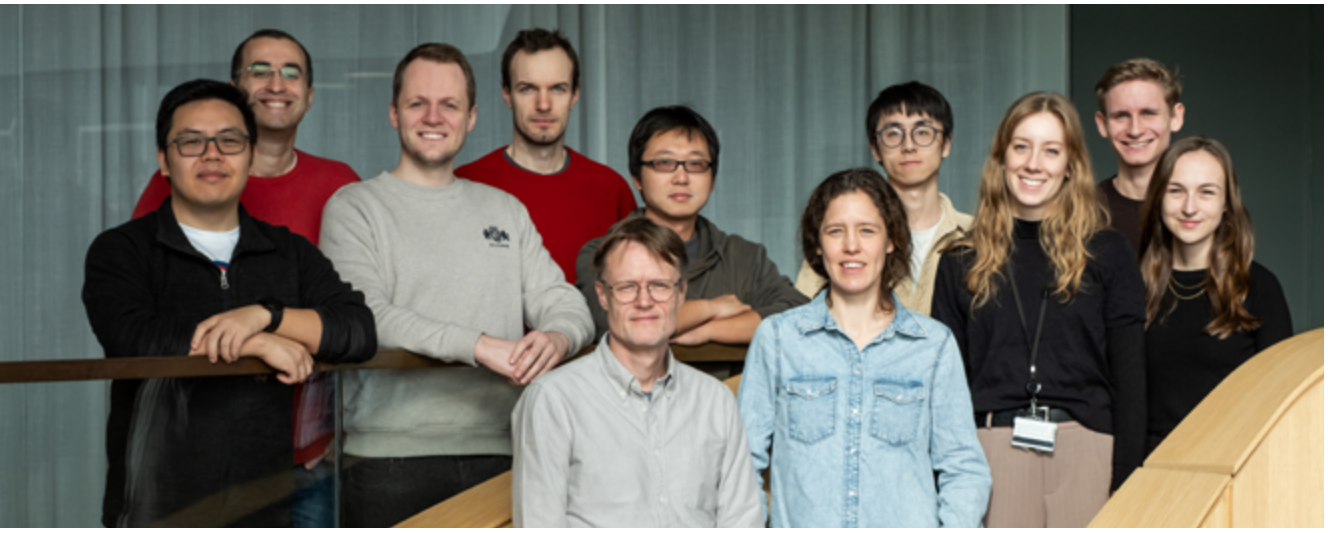
In 2024, we welcomed PhD student Mariana Bronze, who is investigating the cross-activation of specific T cell clones in psoriasis (PS) and inflammatory bowel disease (IBD). This project, in collaboration with Professor Jakob Sedelin (Rigshospitalet), aims to determine whether PS patients develop pathological immune cell populations in the colon, contributing to an interplay between skin inflammation and (subclinical) intestinal inflammation. Epidemiological studies have established a strong link between PS and IBD, and recent genetic research suggests shared susceptibility factors. However, the underlying mechanisms remain poorly understood.
To address this, we are employing multiparameter flow cytometry, proteomics, and single-cell RNA sequencing (scRNAseq) to profile key inflammatory markers and immune cell populations in both skin and colon samples. One of our key objectives is to compare immune signatures between PS, IBD, and PS/IBD overlap patients to identify common inflammatory pathways. Additionally, we are investigating whether T cells migrate between the gut and skin by assessing shared T cell clonality using scRNAseq. Preliminary transcriptomic analyses indicate an upregulation of gut-homing molecules in PS skin lesions and skin-homing molecules in IBD colons, supporting our hypothesis.

Throughout 2024, the group actively engaged in international collaborations and conferences, presenting our findings on immune regulation and barrier immunology. We look forward to further advancing our research in 2025, strengthening our collaborations, and exploring new therapeutic avenues to improve the treatment of inflammatory and immune-mediated diseases.



Molecular Immunology and Inflammation

The Molecular Immunology and Inflammation Basic Research Group focuses on understanding the fundamental processes that control immune responses, with a particular focus on molecular mechanisms governing inflammatory signalling and innate immunity. We aim to advance our understanding of the molecular aetiology of inflammatory skin diseases and other immune disorders, which ultimately may pave the way for improved treatment strategies.



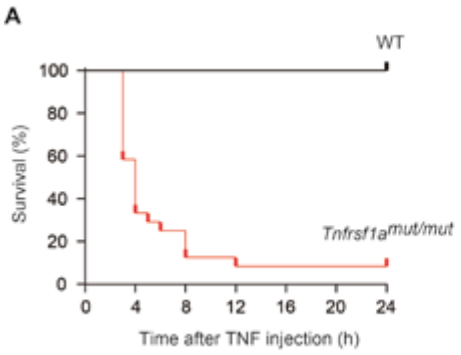
A central focus of the group is to understand the molecular mechanisms that regulate signal transduction by immune receptors and how they impinge on immune responses and inflammation *in vivo*, with a particular focus on Met1-linked ubiquitin chains generated by LUBAC (Linear ubiquitin chain assembly complex). For this, we employ genetic engineering of cell culture systems and we have generated novel genetically-modified mouse models that are being extensively characterised in different experimental inflammation and infection models. Complementing our murine in vivo models, we are excited to also implement state-of-the-art 3D human epidermal skin models, which will be established at SIC through a Leo Foundation grant for SIC. This will enable us to address the translatability of our findings in murine models in genetically modifiable ex vivo human skin-like models and thereby to obtain novel insights into the pathological molecular mechanisms underlying human inflammatory skin diseases.

2024 has been an exciting year for the group where we have seen the publication of several studies we have contributed to, including studies on the role of the ribotoxic stress response pathway in coordinating inflammation in the skin following UV damage (Vind et al. *Mol Cell* 2024), the role of Met1-linked ubiquitin chains in driving inflammatory signalling in cells in response to mitochondrial damage (Vringer et al. *EMBO J* 2024), and the first characterisation of a small-molecule RIPK1 degrader (PROTAC) in regulating cell death, antitumour immunity and skin inflammation (Mannion et al. *Immunity* 2024).

In addition, we have submitted the first manuscripts based on SIC-developed projects and have advanced our on-going research projects relating to the role of Met1-linked ubiquitin in immunology. In one of the submitted studies, we describe a novel and unanticipated mechanism that determines the capacity of tissues/organs to respond to the proinflammatory cytokine TNF (tumour necrosis factor). Our work describes an evolutionarily conserved regulatory element in the *TNFRSF1A* gene that limits the translation of the *TNFRSF1A* mRNA and thereby controls the abundance of TNF Receptor 1 (TNFR1) in cells. Consequently, the regulatory element determines to what extent tissues activate an inflammatory response when exposed to TNF and mutation of the element in mouse models resulted in extensive pathology and lethality to levels of TNF that are normally well-tolerated (Fig 1). Exemplified by the TNF-TNFR1 system, our findings suggest that the cytokines produced by immune cells may not be the sole cause of pathological inflammation in tissues, but that dysregulation of the cognate receptor is involved in the pathogenesis by enhancing the tissue-response to immune-derived cytokines. We speculate that this could be involved in the establishment of chronic inflammatory conditions such as psoriasis and inflammatory bowel disease. This concept will be investigated further in future work.

The group has also been engaged in several education and research dissemination activities. I and other members of the group have presented our research at several research meetings and institutions in Denmark and internationally, including at the University of Cologne and University of Aarhus and at the EMBO Workshop on Pathogen Immunity and Signalling in Venice, Italy – a meeting I co-organised for the third time together with several international colleagues. The meeting received widespread attention by the research community, and we were invited to write a meeting report in *Nature Immunology* (Gyrd-Hansen et al. *Nat Immunol* 2024). I also co-organised the annual SIC Springtime School held in Hornbæk and together with Beatrice Dyring-Andersen organised the second "Skin Proteomics and Immunology" symposium held in the Mærsk Tower. Our education activities include running the MSc course "Chronic Inflammation and Autoimmunity - From Basic Research to Therapy" and the PhD course "Mechanisms in Innate Immune Signalling", along with lectures on several other courses run by the department.

A central focus for 2025 will be to publish the submitted manuscripts and to submit additional manuscript on the role of Met1-linked ubiquitin in immunology and skin inflammation. Another focus will be to move forward with the implementation of the 3D human skin model to complement our in vivo murine skin inflammation projects. The year will also see three of our PhD students finalise their project and submit their PhD thesis, and I expect to welcome new members in the group towards the end of the year.



Legend: (A) Survival curve and (B) H&E and cleaved caspase-3 (apoptosis) stain of mouse liver sections of mice challenged by TNF injected intraperitoneally. Mutation of a regulatory element in Tnfrsf1a (mut) renders mice intolerant to doses of TNF that do not cause toxicity in WT mice. Data by Biao Ma / Majken Kjær

Translational regulation of TNFR1 levels determines the tissue tolerance to TNF *in vivo*

Skin Inflammation and Cancer

The Skin Inflammation and Cancer research group at SIC investigates the mechanisms underlying chronic skin inflammation and the role of bacteria in disease progression and treatment resistance in cutaneous T cell lymphoma (CTCL) and atopic dermatitis (AD). Although driven by malignant and non-malignant $CD4^+$ T cells, respectively, these diseases share numerous clinical and histopathological features, including susceptibility to disease exacerbation by Staphylococcus aureus.

Our current research primarily focuses on:

- The interplay between pathogenic $CD4^+$ T cells and the lesional microenvironment
- The role of S. aureus in modulating inflammatory processes and driving disease progression
- The identity and functional properties of pathogenic $CD4^+$ T cells

Key Findings in 2024

This year, we have explored why CTCL patients exhibit increased susceptibility to *S. aureus* colonisation and how bacterial toxins influence malignant T cells, the tumour microenvironment, and the skin barrier. We discovered that *S. aureus* and its superantigens (SEs) induce resistance to cancer-drugs in malignant T cells - an effect that could be reversed using antibiotics and non-antibiotic antimicrobial enzymes, specifically bacteriophage-derived endolysins (Vadivel CK et al., *Blood*, 2024).

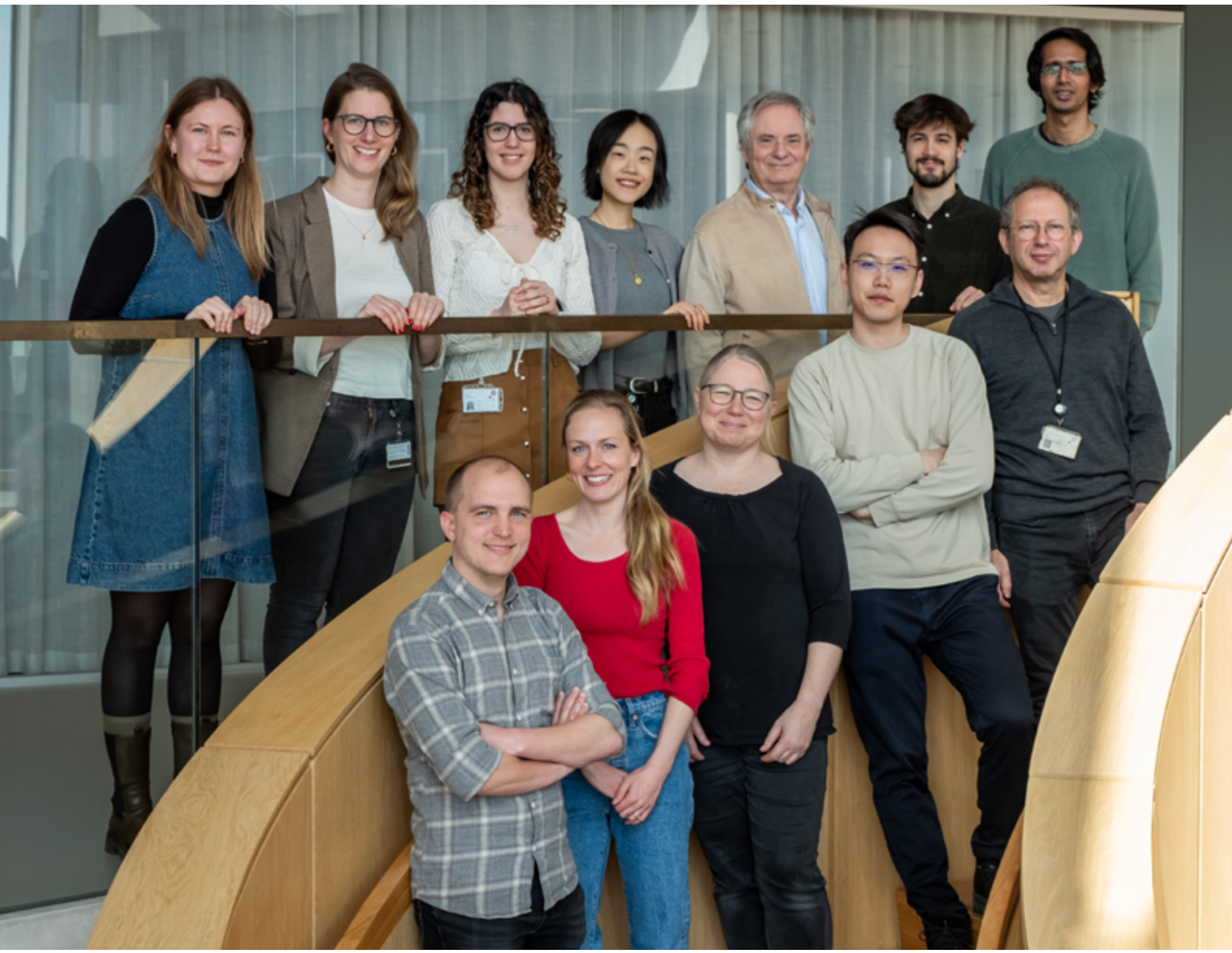
In parallel, we identified a subpopulation of keratinocytes in lesional skin that express MHC class II molecules, enabling SE presentation and subsequent cytokine release by both malignant and non-malignant T cells. This cytokine release further upregulates MHC class II expression in keratinocytes, amplifying SE presentation, cancer cell proliferation, inflammation, and repression of filaggrins - perpetuating a vicious cycle of skin barrier dysfunction. Notably, antibiotic treatment of patients with *S. aureus*-colonised skin lesions inhibited MHC class II expression and improved skin barrier protein levels, underscoring its clinical significance (Zeng et al., JID 2024; Gluud et al., submitted; Namini et al., in preparation).

Collectively, our findings indicate a novel role of S. aureus in cancer-drug resistance and skin barrier deterioration, potentially explaining its association with disease activity and progression. Encouragingly, our research has contributed to updates in European EORTC guidelines for CTCL treatment and care. Furthermore, we have filed a patent on the use of endolysin-based therapies for CTCL.

A Novel Perspective on Cancer Subclones and Treatment Resistance

Our most recent breakthrough concerns the discovery of multiple genetically distinct cancer subclones in most patients with cutaneous lymphomas. Importantly, despite genetic differences, all cancer subclones within a single patient express identical T-cell receptors (TCRs) yet exhibit distinct responses to external stimuli, including cancer-drugs and *S. aureus*. This suggests that tumour heterogeneity enables cancer cell populations to adapt and evolve within the tumour microenvironment. Additionally, our findings reveal an important mechanism by which bacteria contribute to disease progression – by selectively expanding *aggressive* subclones. This may also provide insight into how treatment resistance emerges, as certain subclones may be preferentially selected under therapeutic pressure (Buus et al., Cancer Discovery, in revision).

These findings underscore the necessity of subclonal analysis to combat treatment resistance, which typically develops rapidly in advanced-stage patients, contributing to poor prognoses.



New Research Initiatives in 2024

In addition to our ongoing work, we have initiated several new lines of research, including:

- Development of a novel cancer cell-targeted treatment model
- Characterisation of *S. aureus* strains isolated from CTCL and AD patients across different disease stages
- Investigation of bacterial regulators of virulence factors and toxins (e.g., SEs), aimed at identifying novel small-molecule inhibitors
- Discovery and evaluation of new endolysins for their efficacy in mitigating *S. aureus*-mediated immune dysregulation and disease exacerbation in AD and CTCL

Team Expansion and Key Appointments

A highlight of the year was the expansion of our group, including the recruitment of microbiologist Assistant Professor Lene Bay, the return of Professor Thomas Litman from New York, and the establishment of a new research team (within Skin Inflammation and Cancer) by Dr. Abildgaard Fellow Terkild B. Buus.

T Cell Biology and Skin Inflammation

The T Cell Biology and Skin Inflammation Basic Research Group investigates T cell activation, differentiation and effector functions as key factors in the development and treatment of inflammatory skin disease. The group is headed by Professors Charlotte Menné Bonefeld and Carsten Geisler.

The focus of the group is to improve the understanding of the role of T cells in inflammatory skin diseases and in skin homeostasis. The group aims to advance the knowledge of:

- immune responses against clinically relevant contact allergens, both against single allergens and allergen mixtures,
- different subsets of epidermal T cells, including their developmental trajectories and function, in both healthy and inflamed skin,
- the impact of age and skin type on immune responses in the skin.

In 2024, the group has investigated how $CD8^+$ epidermal-resident memory T (TRM) cells affect the skin barrier. Dysfunction of the skin barrier is regarded as a key event in the initiation and progression of inflammatory skin diseases. In many cases of allergic contact dermatitis (ACD), $CD8^+$ TRM cells play a central role in the immune response to contact allergens. However, if and how allergen-specific $CD8^+$ TRM cells affect the expression of skin barrier molecules is not known. We found that $CD8^+$ TRM cells contribute to a prolonged reduction in the expression of skin barrier molecules, which might exacerbate allergen permeation and the inflammatory response during succeeding

exposures of the skin to allergens and antigens (Vaher et al., 2024).

We extended our study on the role of pre-existing skin inflammation in the response to new contact allergens. It is still a major question whether patients with atopic dermatitis (AD) have an altered response to contact allergens compared to controls without AD. To address this question, we compared the response to the contact allergen 1-fluoro-2,4-dinitrobenzene (DNFB) in wild-type (WT), $Flg^{ft/ft}$ and $Tmem79^{ma/ma}$ mice in a well-established model for ACD. WT mice represent healthy skin, $Flg^{ft/ft}$ mice represent skin with an impaired skin barrier without skin inflammation, and $Tmem79^{ma/ma}$ mice represent skin with impaired skin barrier and pre-existing skin inflammation. Surprisingly, we found that pre-existing skin inflammation, as seen in AD patients, can result in anti-inflammatory mechanisms that suppress immune responses to new allergens/antigens (Jee et al., 2024).

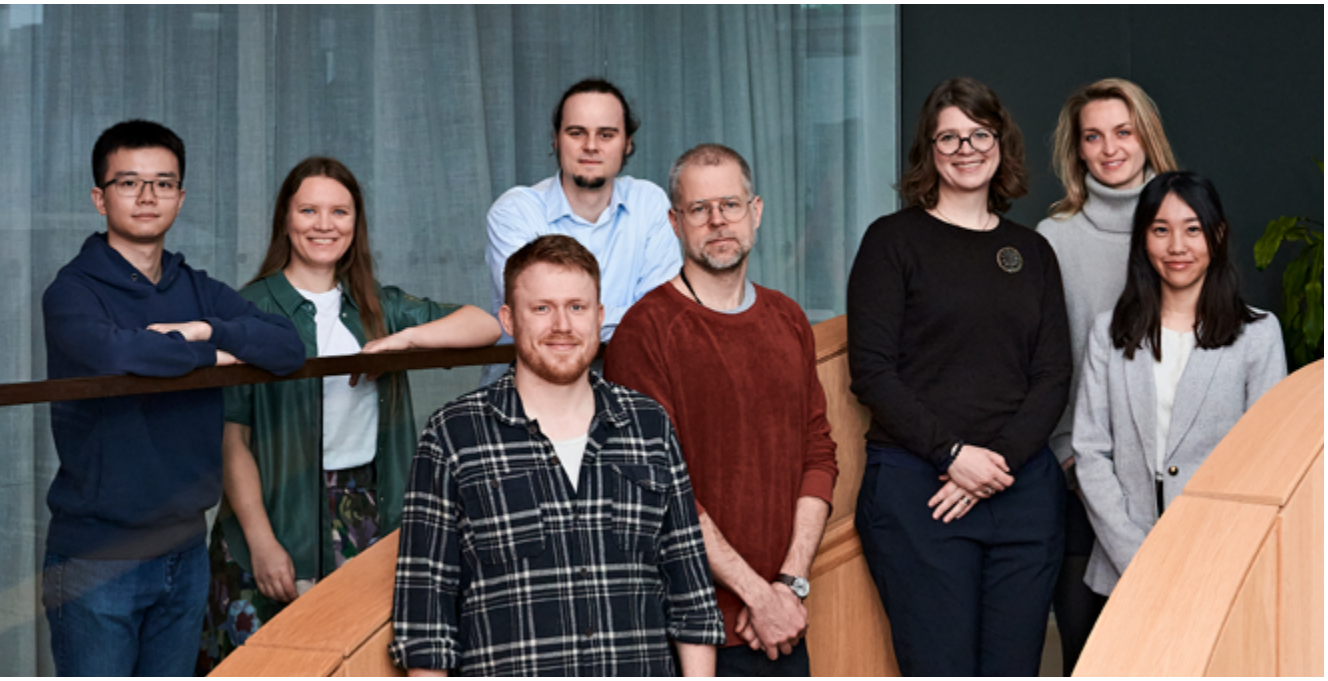
We furthermore concluded our studies on the regulation of immune response genes in the skin of allergic and clinically tolerant individuals exposed to the hair dye p-phenylenediamine (PPD). PPD is a potent contact allergen found in many hair colour products. However, not all individuals develop ACD although they are regularly exposed to PPD. It is unclear whether these asymptomatic individuals are true non-responders to PPD or whether they mount a response to PPD without showing any symptoms. We performed RNA sequencing on skin biopsies from 11 asymptomatic hairdressers regularly exposed to PPD and from 10 individuals with known ACD to PPD four days after exposure to PPD. We found up-regulation of several genes in both asymptomatic and allergic individuals, demonstrating that there are no true non-responders to PPD but that the immune response elicited by PPD differs between individuals and can lead to either tolerance, subclinical inflammation or allergy (Meisser et al., 2024).

We extended our studies on contact allergy in African countries. We recently found that chromium is a common contact allergen identified by patch tests in African countries. Cement is an important source of chromium exposure. Since 2005, cement may not be used in countries of the European Union (EU) if the concentration of hexavalent chromium (Cr(VI)) is >2 mg/kg, which has significantly reduced the prevalence of ACD caused by cement in EU. To determine whether Cr(VI) in cement could be a contributing cause to the high prevalence of ACD to chromium in African countries, we performed analyses of total chromium (Cr) and Cr(VI) in eight random samples of cement purchased in three African countries. We found that the content of Cr(VI) in six out of the eight samples was ≥16 mg/kg, that is, more than eightfold higher than the maximal allowed concentration in the EU (Bonefeld et al., 2024). This indicates that a targeted effort in reducing the concentration of Cr(VI) in cement coupled with measures to prevent direct skin contact with cement could considerably reduce chromium allergy in at least some African countries.

To determine the prevalence and immunological phenotype of ACD in Tanzania, we have initiated a collaborative study with Professors Elisante John Masenga and Daudi Mavura and PhD student Herielly Ombeni Msuya, Regional Dermatology Training Centre (RDTC), Kilimanjaro Christian Medical Centre (KCMC), Moshi, Tanzania.

In 2024, Kelvin Yeung graduated as PhD, Tiana Ida Stanisic and Alexandra Teresa Seibel as Master in Immunology and Inflammation from our group. Martine Dragsbæk-Friis and Simone Stegenborg-Grathwohl started as PhD students and William Steiner Olsen as Master student in our group. Furthermore, we had the great pleasure of having Herielly Ombeni Msuya from RDTC and Mikkel Bak Jensen from BIOSKIN as guest researchers in our group.

Translational Skin Immunology



The Translational Skin Immunology Group studies the composition of localised disease memories in psoriasis and vitiligo to identify new targetable mechanisms of skin pathology that would enable long-term clinical remission.

Despite a rapid development of highly effective biologic treatments for diseases such as psoriasis, the rapid relapse of disease following cessation of therapies remains a clinical problem at high costs. The Translational Skin Immunology group was established in 2021 to detangle the components of T cell driven local relapse. Local relapse is common in a number of inflammatory skin diseases such as psoriasis, vitiligo and contact allergies, where molecular scars in resolved skin lower the threshold to recurrent inflammations.

Disease-driving T cells resident within the skin, primarily in the epidermis, maintain pathogenic profiles years after disease resolution in resolved skin. These skin resident memory T (Trm) cells act as rheostats for inflammation in the human epidermis and by understanding how these cells are maintained and regulated, new therapies aiming at deep remission of focal inflammatory skin diseases would be feasible.

Through work at the Eidsmo laboratories in Stockholm and in Copenhagen, a small population of local precursor cells within the human skin, that following stimulation mature to Trm cells was identified. Local disease-driving Trm-cell precursors would explain why localised disease memories persists for years following disease resolution. To understand how pathogenic Trm cells are maintained and propagated in resolved lesions, a collaboration with BIOSKIN was initiated in 2023. During 2023-24, spatial transcriptomics was used to analyse 80 samples from 16 individuals with untreated psoriasis or resolved disease following treatment with TNF, IL-17 or IL-23 blockade. The preliminary data is exciting with normalisation of the disease-associated cytokines IL-17 and IL-23, but nevertheless distinct retained molecular dysregulation in both the immune and stromal compartment.

Another clinical dilemma that has been addressed by two BRIDGE fellows in the group is the lack of biomarkers and tools to predict whether inflammatory skin diseases will progress or relapse following cessation of treatment. Albert Duvetorp has collected patient data from several thousands of people living with psoriasis in Denmark, Sweden, the Netherlands and Chile. Albert is now analysing triggers of psoriasis and is testing whether local biomarkers can predict if physical stimulation of the skin lead to induction of new psoriasis plaques.

Rune Kjærsgaard Andersen has truly fulfilled the vision of the Translational Skin Immunology group in his impressive studies using national registers in Denmark, cohorts of patients in Roskilde and genetic analysis in collaboration with DeCode in Iceland, thereby identifying both life-style factors and WNT signalling as a potential disease drivers in Hidradenitis supporativa.

As Liv Eidsmo decided to take up a new role as Chair of Dermatology and Venereology at Karolinska Institutet and University Hospital in Sweden, the Translational Skin Immunology Group is closing in SIC. The true impact of research is training the next generation and will be exciting to follow the past and present members that were trained in the exciting scientific community at SIC.

BIOSKIN

With biological samples and clinical data from some 1,300 patients and counting, the Copenhagen Translational Skin Immunology Biobank and Research Program (BIOSKIN) is an internationally leading biobank for skin diseases.

"Adding to the value of the biobank is the fact that participants are followed over long time. This will allow us to detect patterns that are not apparent at the first contact. For instance, what characterizes patients who develop severe illness? By identifying people who are at high risk, we aim to treat them early avoiding that they contract severe chronic disease," says Jeanne Duus Johansen, Clinical Professor at BIOSKIN, adding:

"Of course, it is not always possible to prevent disease. We are also strongly engaged in development of new treatments. But contributing to prophylaxis is our top priority."

Revealing interlinked health issues

A part of the prophylactic approach is to identify patients at risk of co-morbidities. In recent years it has transpired that skin diseases may be associated with diseases elsewhere in the body. As examples, psoriasis patients have increased risk of certain cardiac disorders, while atopic dermatitis patients can be more exposed to allergies and asthma.

"If we can spot early on, which patients are at risk of co-morbidities, we might be able to prevent such additional health problems," says Marianne Bengtson Løvendorf, Head of Research at BIOSKIN.

While the patients are obviously the first to benefit from avoiding co-morbidities, the Danish society and healthcare system may also benefit in terms of healthier citizens and lower costs for treatment.

The willingness to participate is high

BIOSKIN was established in 2021 at Herlev-Gentofte Hospital through an add-on grant from the LEO Foundation to the Skin Immunology Research Center (SIC) at the Panum Institute. The goal is following 3,000 patients with the most prevalent chronic inflammatory skin diseases: psoriasis, atopic dermatitis, and contact eczema.

Patient inclusion started 2022 and by the end of 2024, a total of 1,296 patients were included. The number is steadily increased, since all new patients in the relevant groups admitted to the hospital's Department of Dermatology and Allergy are invited to participate.

"Most patients agree to participate right away. Some decline, usually when they hear we need about an hour of tests and data collection for the initial registration. Quite often, however, they come back later to be included," reports Marianne Bengtson Løvendorf.

After the initial session, each patient will be invited to a follow-up after 3, 6, 9, and 12 months, and hereafter a yearly session. Should a major change happen, such as more severe disease development or introduction of a new treatment, the biobank will invite the patient to start over. Meaning a new lengthy session and follow-ups after 3, 6, 9, 12 months etc.

SIC and BIOSKIN as a perfect match

From the outset, BIOSKIN has operated in close collaboration with SIC. This is a perfect match, according to Marianne Bengtson Løvendorf:

"We provide samples and clinical data which are highly valuable to the academic researchers at SIC, while they contribute with expertise not least at the molecular level. The combination holds great potential. The skin and associated diseases have been investigated and described

The BIOSKIN program is anchored at the Department of Dermatology and Allergy, Herlev-Gentofte Hospital where it since its commencement of inclusion of patients in 2022, has been integrated into the daily clinical practice.

for more than 100 years, but only now have we acquired the technologies which allow us to understand the involved mechanisms in detail."

Examples of new methods revolutionising the field are RNA sequencing and Spatial Transcriptomics.

"We can rely on the SIC researchers to always be "on the beat" when it comes to new developments in equipment and methodology. Thereby we can devote ourselves to the clinical side. This results in ongoing mutual inspiration," says Jeanne Duus Johansen.

The interplay sometimes happens formally with joint workshops and meetings, but more often informally with ideas exchanged over mail or phone calls. Not least PhD Students serve as nodes of knowledge exchange. Currently the biobank employs 6 PhD Students. All are supervised by researchers at Herlev-Gentofte Hospital and co-supervised by researchers at SIC.

Lone Skov the other clinical professor at BIOSKIN adds: "The possibility of following several large groups of patients with inflammatory diseases for a longer period, together with the close collaboration with basic researchers, makes BIOSKIN a unique project."

Giving back to patients

A new development at BIOSKIN in 2024 was the development and construction of a new website targeted at patients.

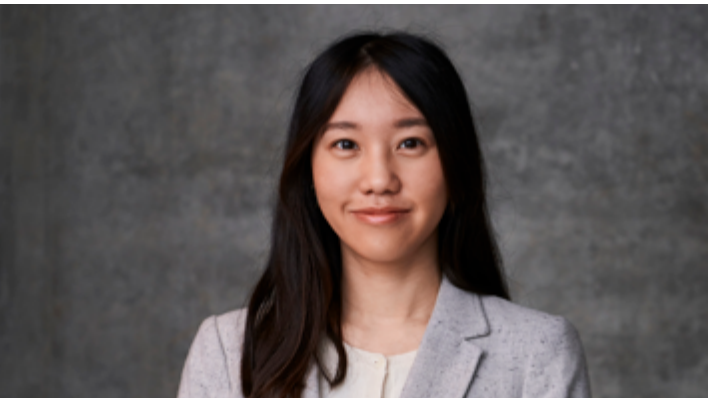
"The patients provide us with a valuable resource in terms of their samples, their data, and their time. We owe it to them to give them something in return. Of course, improved treatment and prophylaxis has the highest value for them, but we also want to show how their contributions help acquire better understanding of skin diseases," says Jeanne Duus Johansen.

The new website, www.bioskin.dk aimed at psoriasis, atopic dermatitis, and contact eczema patients will be introduced in 2025.


Gloves
Excellent
Gloves / Nitrile
Excellent

Education and career development

BLOOD SAMPLES AS TOOLS IN SKIN DISEASE DIAGNOSIS



Combining skin immunology with advanced computation, Dr. Wenning Zheng opens up a new research frontier for SIC. With support from a LEO Foundation Dr. Abildgaard Fellowship, she is establishing her own research team within the Allergic Inflammation group. Her research will utilise blood samples from patients with atopic dermatitis (AD), psoriasis and the joint disease, psoriatic arthritis, to lay the foundation for more efficient diagnosis and treatment.

"The current treatment for skin diseases may seem effective in the short term, but often the disease returns and may even pop up at new sites. Memory T cells already living in the skin have been known to contribute to this relapse, but the appearance of new skin lesions after treatment suggests that these T cells may be moving through the body via the bloodstream. We are interested in identifying the skin diseases-causing T cells in the blood, so that we may track whether they are responsible for new skin lesions, or for new manifestations of the disease, like psoriatic arthritis", explains Wenning.

"Blood samples are easier to collect and less invasive than skin biopsies, making them a valuable resource. By finding these specific T cells, we hope to help diagnose and treat skin conditions earlier and more effectively," she adds.

As a first step, Wenning will perform single cell sequencing using donor-matched skin and blood samples. She will use a unique cell specific ID called the 'T cell receptor' to map clones of T cells that circulate between the skin, blood and other organs.

LONG-TERM STUDY UNDERWAY

Previously a postdoctoral researcher in the Translational Skin Immunology group at SIC, Wenning was awarded a LEO Foundation Dr. Abildgaard Fellowship to support her innovative research. Named after the founder of the LEO Foundation, Dr. Knud E. Abildgaard, the fellowships support talented, emerging research leaders who are ready to establish or expand their own research teams at Danish institutions.

"In my former group, I have demonstrated that clones of T cells found in healthy human skin can also be found in the blood. This implies that clones of T cells found in diseased skin may also make their way into the circulation and serve as tools to track disease progression. This fellowship allows me to investigate blood T cell clones in patients suffering from various skin diseases and may lead to future therapeutic applications," she says.

The project will begin with a 2- to 3-year study profiling T cell clones in patients with AD and psoriasis. Long-term studies are necessary, Wenning emphasises:

"Moving forward, we will show the relevance of these specific blood T cells in large cohorts to prove that the blood can be used to diagnose and monitor skin diseases over time", says Wenning Zheng.

MACHINE LEARNING AND ADVANCED ASSAYS TO IDENTIFY ANTIGENS THAT TRIGGER T CELLS

In addition to tracking clones of T cells in patients with skin diseases, Wenning's research will also tackle another complex question: What antigens do these T cells recognise that cause them to induce inflammation in the skin? This again relates to the T cell receptor, since this molecule senses peptide antigens in the environment.

Here, Wenning will lean on her impressive computational background and machine learning approaches to identify candidate antigens that may trigger the activity of these T cell clones. She will use available immune epitope databases to delve into this problem.

In collaboration with Jonathan Coquet, Wenning will validate the antigen reactivity of these clonal T cells using T cell stimulation assays and sensitive reagents that are designed to specifically detect these clonal populations of T cells.

LOOKING FOR COMORBIDITY MECHANISMS

Beyond serving as an alternative to skin biopsies, blood sampling offers new opportunities to understanding disease mechanisms. Having different types of tissue samples (skin, blood, joints) available will open doors to better understanding disease mechanisms and may help to explain known comorbidities of people with skin diseases:

"T cells in the blood are more mobile than those in the skin. For example, a frequent comorbidity for psoriasis is psoriatic arthritis. If we can pinpoint the exact T cell type which causes the skin disease, and if we can find this clone elsewhere in the body – for psoriatic arthritis patients in the joints - this could explain existing comorbidities or provide early warning of potential issues."

The blood and skin samples of patients with AD or psoriasis will be provided through a collaboration with the Copenhagen Translational Skin Immunology Biobank and Research Program (BIOSKIN), Herlev-Gentofte Hospital, with single cell sequencing being performed at SIC. The psoriatic arthritis project is a collaboration with Liv Eidsmo's group at the Karolinska Institutet in Sweden.

"I will include publicly available single cell datasets into our study to increase the sample size and enable benchmarking. As a trained bioinformatician, I will perform this integrated analysis using a workstation. To enhance work efficiency, high-performance computing infrastructure like Computerome will also be useful," says Wenning.

IMPLICATIONS FOR TREATMENT

Wenning aims to demonstrate that our blood is an effective window to understanding our skin. Identifying blood biomarkers can help both academic researchers and clinicians monitor disease development in patients with greater precision.

"Since my previous work has shown that blood can provide valuable insights into the health of human skin, I now aim to establish that blood can also serve as a useful tool to understanding the status of people with skin diseases. By examining blood markers, we may be able to offer a less invasive clinical method for monitoring a patient's disease progression over time." explains Wenning.

Ultimately, the research could lead to more targeted treatments. "Targeting a range of different T cells may improve the patient's condition but also come with risk of side-effects. If instead we can target only the specific T cell type causing the disease, this would be a significant improvement," she concludes.

SPRINGTIME SCHOOL 2024
EXPLORING INFLAMMATION ACROSS BARRIER ORGANS

Each spring, SIC welcomes early-career researchers from around the world to its annual Springtime School. The 2024 edition, held in the quaint seaside town of Hornbæk on the scenic northern coast of Zealand, focused on "Mechanisms of inflammation in skin and other barriers".

Supported by an add-on grant from the LEO Foundation, the conference offered a high-level scientific programme and an inspiring setting for exchange and collaboration. Now an established event in the skin immunology calendar, Springtime School is increasingly recognised as a leading conference for young researchers, attracting a high number of applications and drawing scientific talent from across Europe, North America, Asia, and Australia.

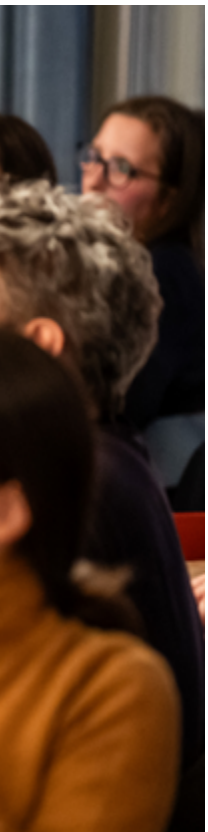
The programme featured a wide range of talks delivered by 12 invited speakers, exploring immune responses in the skin, gut, and other barrier organs, spanning topics such as tissue-resident lymphocytes, microbial interactions, translational immunology, and molecular mechanisms of inflammation. The programme also included short talks by early-career researchers, flash talks, and poster sessions, encouraging knowledge sharing and dialogue across career stages.

The unique coastal setting created an ideal backdrop for scientific discussion, informal networking, and new collaborations. Time spent together over shared meals, walks, and social activities contributed to a vibrant and collegial atmosphere that extended beyond the formal sessions.

Springtime School continues to be a cornerstone in SIC's commitment to supporting the next generation of researchers and advancing the understanding of skin immunology and barrier-related disease mechanisms.

Organising committee
Liv Eidsmo, Jonathan Coquet, Mads Gyrd-Hansen, Hannah Paludan

In 2025, the conference will return to its former name — Summer School — and will take place from 12th–14th of May 2025.



SPEAKERS AND TITLES OF TALKS AT SPRINGTIME SCHOOL 2024

- Laura Mackay, The Peter Doherty Institute, University of Melbourne, Australia: *Diversity of tissue-resident lymphocytes*
- Shawn Demehri, Harvard Medical School, USA: *Control of Malignant Clones by Antiviral T Cells in the Skin*
- Bill Agace, SIC, University of Copenhagen, Denmark: *Tracking adaptive T cell responses in the healthy and inflamed human intestine*
- Eduardo Villablanca, Karolinska Institutet, Sweden: *Unravelling the Cellular and Molecular Architecture of the Healing Intestinal Barrier*
- Henrik Nyhus Kløverpris, ISIM, University of Copenhagen, Denmark: *Breaking Barriers in HIV: Impact on Immune Reconstitution and Intestinal Stem Cells*
- Simon Bekker-Jensen, University of Copenhagen, Denmark: *Skin responses to UV-irradiation and other insults: Critical roles for ribosomes in sensing of cell stress*
- Jürgen Ruland, Technical University of Munich, Germany: *Mechanisms of MALT1 signalling in skin inflammation*
- Heidi Kong, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH in Bethesda, Maryland, USA: *The Human Skin Microbiome in Eczematous Skin*
- Salomé Leibund Gut-Landmann, University of Zürich, Switzerland: *Skin commensal fungi in health and disease – a matter of tissue context and immunity*
- Gregor Jemec, University of Copenhagen & Zealand University Hospital, Denmark: *Dermatoiconography - what dermatology is really about*
- Christoph Schlapbach, Bern University Hospital, Switzerland: *Pathogenic Th2 cells in skin inflammation*
- Niroshana Anandasabapathy, Weill Cornell Medicine, USA: *Organismal DC differentiation balances tissue and tumour immunity and tolerance*

YOUNG INVESTIGATOR NETWORK
BRIDGING ACADEMIC AND CLINICAL SKIN RESEARCH

The Young Investigators Network (YIN) brings together early-career researchers across academic and clinical dermatology to strengthen collaboration and mutual understanding.

Established in 2019, the network has become a well-established platform for building bridges between basic and clinical skin research in the Copenhagen area.

Through regular events, institutional visits, and professional development activities, YIN continues to create opportunities for knowledge exchange and collaboration across disciplines. In 2024, one of the key activities took place at the Department of Dermatology and Allergy, Herlev-Gentofte Hospital, where members of the network — both academic researchers and clinicians — had the opportunity to observe clinical consultations with patients living with psoriasis. This encounter with everyday clinical practice offered valuable insight into the lived experience of disease and contextual factors influencing disease progression.

"Clinical researchers interviewed patients with psoriasis in plenum. This was a valuable experience for us in academic research. Obviously, we know well from textbooks how factors such as stress, alcohol intake, overweight, and physical inactivity may influence psoriasis developments. Still, it is quite an eye-opener to hear patients tell their stories," says Martin Kongsbak-Wismann, Associate Professor at SIC and Chair of YIN.

"As academic researchers, we mostly look at artificial biological systems such as cell lines, etc. But sometimes we also analyse human samples from biopsies or skin tape strip samples. It is highly relevant that we also connect to clinical reality, learning what lies behind the decision to do a biopsy, for instance. On the other hand, clinical researchers will also benefit from getting to learn how things look from our side. To take an example, how does the size of a skin biopsy or the number of sequential skin tape strips influence the value of the samples to us?"

Several collaborations have emerged through the network. One current project, initiated after a YIN event in 2023, involves the extraction of lipids, protein and RNA from skin tape strip samples from patients with chronic hand eczema — a joint effort between Martin Kongsbak-Wismann, clinical researcher Marianne Bengtson Løvendorf from BIOSKIN at Herlev–Gentofte Hospital, and dermatologist Caroline Meyer Olesen from Bispebjerg Hospital.

"It is just much easier to initiate a collaboration when you know whom to contact and also have an understanding of the conditions at both the academic and the clinical side," says Martin.

"Providing this understanding is our primary purpose. When joint research projects emerge, this is an important bonus."

In 2024, YIN also welcomed new members from the LEO Foundation Center for Cutaneous Drug Delivery (LFCCDD) at the Department of Pharmacy, University of Copenhagen. The center contributes expertise on the skin as a barrier for drug absorption and the properties of drugs and excipients in delivery systems. During a visit, members were introduced to the center's technologies and methods — a valuable complement to SIC's research on novel treatments.

"Since our research here at SIC is often focused on potential drugs for skin disease treatment, it was obvious to extent the network to include the brilliant researchers from LFCCDD. It goes without saying, that it is highly relevant to collaborate with skin drug delivery researchers," Martin notes.

Institutional visits continue to be a key component of YIN's activities. In 2024, events were hosted at SIC, Herlev-Gentofte Hospital, and the Department of Pharmacy.

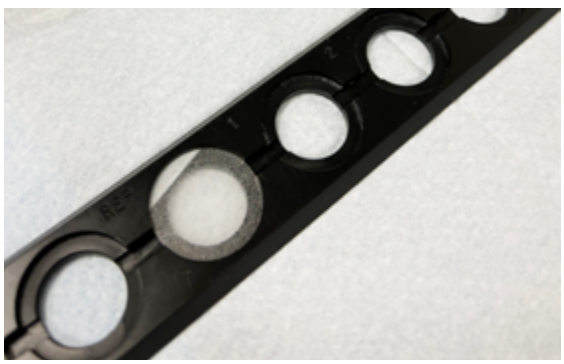
"For a network like YIN, you can never assume that since we did something a few years ago, this has been covered. Many new faces join the network and others leave. If you are a PhD, you will typically be with us for three years," says Martin.

In addition to scientific exchange, YIN also supports broader career development. In 2024, a short course on time management proved highly popular among early-career researchers.

"We got excellent feedback for this event! The course proved an eye-opener to many, especially the new, younger members of the network. Too often as a young professional, you will see time slipping through your fingers due to various distractions," says Martin, noting that participants particularly appreciated the practical tips and strategies shared by the instructors.
With a strong foundation and growing community, YIN continues to provide a valuable platform for connecting disciplines, inspiring collaboration, and equipping the next generation of researchers to thrive.

YIN is always looking for new members; if you are an early-career scientist or doctor working in the cross-field of immunology and dermatology, reach out to us at sic@sund.ku.dk.

Planning committee, 2024
Martin Kongsbak-Wismann - Chair
Berthe Katrine Fiil
Dorra Bouazzi
Jennifer Astrup Sørensen
Martin Rich Javadi Namini
Pernille Lindsø Andersen
Ragna Guldsmed Diedrichsen
Sofia Botvid
Stine Rønholt
Hannah Paludan



To illustrate the size and depth of a skin biopsy, the clinicians at BIOSKIN demonstrated this very elegantly using a banana. Likewise, the tape stripping method was showcased on a volunteer, and it was shown how protein concentration could be determined subsequently by Squame Scan measurements.

PROTEOMICS SYMPOSIUM

Following on from the success of the first Proteomics Symposium held in 2023, Professor Mads Gyrd-Hansen and Associate Research Professor Beatrice Dyring-Andersen organised in 2024 the symposium "Proteomics in Dermatology and Immunology v2.0", which took place on August 27th at the Mærsk Tower where SIC is also situated. The symposium brought together national and international experts in proteomics to share their insights, featuring excellent talks and networking opportunities during the coffee breaks to promote collaboration and knowledge sharing. The symposium commenced with a warm welcome by Beatrice and Mads, who introduced proteomics and how it is advancing our understanding of biological systems, including the skin.

Ali Azimi from the University of Sydney shared their advances on how proteomics of tape strips can be used as a non-invasive method to analyse skin lesions. This was followed by Asolina Braun from Monash University who presented the use of immunopeptidomics of skin for discovery of antigens involved in psoriasis. Giulia Franciosa from the NNF Center for Protein Research at the University of Copenhagen presented her research using phospho-proteomics to delineate the signalling interactions of tumour-infiltrating lymphocytes and cancer cells in melanoma. Max Sauerland from the Molecular Immunology and Inflammation group at SIC gave a methodology talk where he presented an optimised method to retrieve proteins from skin biopsies and showed how this can be used for improved detection of the ubiquitin-modified proteome in the skin. This was followed by a presentation by Neil Rajan from the University of Newcastle, who presented unpublished work where he uses proteomics to understand the signalling alterations in skin tumours from CYLD cutaneous syndrome patients – a familial disease caused by genetic loss of the deubiquitinating enzyme CYLD. The final talk of the symposium was given by Kostas Kalogeropoulos from the Danish Technical University who presented the group's work on using mass spectrometry to elucidate the proteomic and proteolytic landscape of cutaneous wound healing using wound exudates. The symposium had an engaging atmosphere with questions and comments from the attendees and plenty of discussions during the breaks, leading to an interactive and successful event.

GRADUATED PHD, MASTER, AND BACHELOR STUDENTS

PhD students

- Anna Sophie Quaade. *Hand eczema: From molecular fingerprints to population-wide perspectives*. Supervised by Jeanne Duus Johansen and Jacob P. Thyssen
- Chella Krishna Vadivel, PhD title, *A treacherous trio: Staphylococcus aureus infections, Cytokines, and Drug resistance in Cutaneous T cell Lymphoma.* Supervised by Niels Ødum.
- Dorra Bouazzi, PhD title, *Hidradenitis Suppurativa Epidemiology and Subtypes.* Supervised by Rune Kjærsgaard Andersen.
- Gitte Færk, PhD title, *Children with atopic diseases Care pathways, experiences of care and influence on family life.* Supervised by Lone Skov.
- Ines Lecoq Molinos, PhD title, *Exploring immune-modulatory vaccines to target immunosuppressive macrophages in the tumor microenvironment*. Supervised by Niels Ødum.
- Kelvin Yeung, PhD title, *The immunological memory response to contact allergens in allergic contact dermatitis. Exploring the roles of repeated contact allergen exposure & interleukin-1 inhibition in skin-resident memory T cells.* Supervised by Charlotte Menné Bonefeld, Carsten Geisler and Lone Skov.
- Martin Rich Javadi Namini, PhD title, E*xploring the role of reactive oxygen species and oxidative stress in Cutaneous T cell Lymphoma.* Supervised by Niels Ødum and Terkild Buus Brink.

Master students

- Alex B. Nielsen. *Patients with psoriasis have a dysbiotic taxonomic and functional oral microbiota.* Supervised by Lone Skov and Amanda Kvist-Hansen.
- Alexandra Teresa Seibel, Master thesis, T*he role of miR-31 and Il-34 in regulating immune cell responses in allergic contact dermatitis.* Supervised by Charlotte Menné Bonefeld and Helen Vaher.
- Cecilia Egede Medianfar, Master thesis, *Hidradenitis suppurativa does not increase the risk of female infertility - A pilot study conducted amongst 110 dermatological patients.* Supervised by Rune Kjærsgaard Andersen.
- Lang Yan, Master thesis, *Interactions between malignant T cells and Keratinocytes in Cutaneous T cell Lymphoma.* Supervised by Niels Ødum
- Mattia Dervasi, Master thesis, *Examining the functional plasticity of TRM cells in the skin.* Supervised by Liv Eidsmo.
- Sarah Gupta, Master thesis, *Investigating the role of SPATA2 and RIPK2 in Listeria monocytogenes infection.* Supervised by Berthe Katrine Fiil
- Søren Bjerg, Master thesis, *T-cell Receptor Discovery for Adoptive Cell Therapy.* Supervised by Niels Ødum.

Bachelor students

- Anna Kaiser, Bachelor thesis, *Direct effects of statins on the development of resident CD8+ T-cells in vitro.* Supervised by Liv Eidsmo.
- Martha Ellen Meibom, Bachelor thesis, *Research project on HVDRR patients and infectious lung diseases.* Supervised by Martin Kongsbak-Wismann.
- Mathilde Louise Bergholdt, Bachelor thesis, *NOD2 receptorens rolle i den intestinale barrierefunktion.* Supervised by Berthe Katrine Fiil
- Othilia Louise Kragh Halling, Bachelor thesis, *Effekten af vitamin D i behandlingen af tuberkulose.* Supervised by Martin Kongsbak-Wismann.
- Sofie Fogh Gustafsson, Bachelor thesis, *Research project on HVDRR patients and infectious lung diseases.* Supervised by Martin Kongsbak-Wismann.

PHD COURSE
MECHANISMS IN INNATE IMMUNE SIGNALING 2024

In January 2024, Berthe Katrine Fiil and Mads Gyrd-Hansen ran the annual PhD course on *"Mechanisms in Innate Immune Signaling"* comprising 4 full days of lectures and group work.

The course is designed to equip participants with knowledge on innate immune signaling, from microbe detection to signal consequence, be it successful pathogen clearance or – more detrimental – chronic inflammation.

This year, 18 participants attended the course, representing diverse backgrounds – from medical doctors pursuing a PhD to immunologists, microbiologists, and bioinformaticians; some already-experts on innate immune signaling while others had neither prior immunology knowledge, nor direct experience, but with a strong interest strong interest in the field.
To ensure a common foundation, the course began with a series of 'background talks', before delving into more specific subjects.

EXPERT CONTRIBUTIONS AND INDUSTRY PERSPECTIVES

The course featured invited lecturers, including Ieva Bagdonaite from Center for Glycomics, Beatrice Dyring-Andersen from the Center for Protein Research and Herlev-Gentofte Hospital, Mariena van der Plas from, LEO Foundation Center for Cutaneous Drug Delivery and from SIC William Agace. They provided insights insights from their respective areas of expertise, enhancing the academic depth of the programme.

A journal club was incorporated into the course, allowing students to present and critically discuss pre-selected research papers. This provided an opportunity to engage with relevant literature, foster analytical discussions, and enhance interaction among participants.
To connect academic knowledge with industry applications, the course also included contributions from industry representatives. Representatives from Lactobio – now L'Oréal, Søren Kjærulff that use microbes in skin inflammatory states and STiPe therapeutics, that explore STING as a target. These sessions highlighted translational aspects of innate immune signaling and bridged the gap between research and industry.

INTERNATIONAL SPEAKERS AND STUDENT ENGAGEMENT

The course also welcomed international guest speakers, including Charlotte Odendall, King's College London, and Dr Prof Philipp Henneke University of Freiburg. They presented *'Interferon: Tug of War between Host and Pathogen'* and *'Development of innate immunity in barrier tissues'* respectively. These seminars were open to a wider audience and were very well attended. Following their presentations, the speakers engaged in *meet-the-speaker* sessions, offering students the opportunity to ask more in-depth questions and seek career advice.

COURSE IMPACT

The Mechanisms in *Innate Immune Signaling* PhD course provided participants with a broad yet in-depth perspective on innate immune mechanisms and host-microbe interactions. Student feedback was highly positive, reflecting the course's effectiveness in delivering relevant and comprehensive knowledge.

SIC PHD PROGRAMME

This initiative, funded by the LEO Foundation Add-on Grant VI, now has five approved PhD programmes. Recruitment began in 2023, and in late 2024, three candidates had successfully transitioned into the PhD phase. The remaining two candidates have commenced their Research Assistant positions, as part of the programme's structured pathway toward full PhD enrolment. The SIC PhD Programme continues to strengthen our commitment to developing early-career researchers and fostering the next generation of skin immunology experts.

First phase PhD programmes – Research Assistants recruited in 2024:

The role of the Met1-linked ubiquitin machinery in the immune biology of human keratinocytes and fibroblasts.

- Student: Miriam Beichler
- Main supervisor: Professor Mads Gyrd-Hansen (SIC)
- Co-supervisor: Professor Liv Eidsmo (SIC)
- International collaborator: Dr. Florian Schmidt (Inst. of Innate Immunity, University of Bonn).

Role of inflammatory mediators in the formation of local memory to contact allergens.

- Student: Mariana Bronze
- Main supervisor: Professor Anders Woetmann, (SIC)
- Co-supervisors: Professor Charlotte Menné Bonefeld, (SIC), Professor Jakob Seidelin (Department of Gastroenterology, Herlev Hospital), Professor Lone Skov (Department of Dermatology and Allergy, Copenhagen University Hospital Herlev-Gentofte)
- International collaborator: Professor Jean-Frederic Colombel (Director, Leona M. and Harry B. Helmsley Charitable Trust IBD Center; Director, Susan and Leonard Feinstein IBD Center; Icahn School of Medicine, Mount Sinai, New York, NY, USA).

Second phase PhD programmes – now PhD Students:

The interplay between bacteria and cutaneous T cell lymphoma (CTCL).

- Student: Ziao Zeng
- Main supervisor: Professor Niels Ødum (SIC)
- Primary co-supervisor: Associate Professor Jonathan Coquet (SIC)
- International collaborator: Professor Tomas Mustelin (Div. Rheumatology, Dept Medicine, University of Washington, Seattle, USA).

Role of inflammatory mediators in the formation of local memory to contact allergens.

- Student: Simone Stegenborg-Grathwohl
- Main supervisor: Professor Charlotte Menné Bonefeld (SIC)
- Co-supervisors: Professor Carsten Geisler, (SIC), Professor Anders Woetmann, (SIC), Professor Jeanne Duus Johansen (BIOSKIN, National Allergy Research Centre, Department of Dermato- Allergology, Copenhagen University Hospital Herlev-Gentofte)
- International co-supervisor: Professor Cezmi Akdis (Swiss Institute of Allergy and Asthma Research (SIAF), Davos, CH).

Can allergic contact dermatitis be permanently cured?

- Student: Martine Dragsbæk-Friis
- Main supervisor: Professor Carsten Geisler (SIC)
- Co-supervisors: Professor Charlotte Menné Bonefeld (SIC), Professor Niels Ødum (SIC) and Professor Jeanne Duus Johansen (BIOSKIN, National Allergy Research Centre, Department of Dermato-Allergology, Copenhagen University Hospital Herlev-Gentofte)
- International collaborator: Professor Marc Vocanson (Centre International de Recherche en Infectiologie (CIRI), Lyon, France).

SYMPOSIUM
IMMUNOLOGICAL ASPECTS OF CHEMICAL-INDUCED SKIN REACTIONS

Professor Charlotte Menné Bonefeld organised and hosted the symposium "Immunological Aspects of Chemical-Induced Skin Reactions" in May 2024 at the Mærsk Tower. The event brought together national and international experts to share their latest insights into how chemicals trigger immune responses in the skin, providing a robust forum for collaboration and discussion.

Jean-Pierre Lepoittevin from CNRS, Institute of Chemistry UMR 7177, University of Strasbourg, kicked off the symposium by examining how chemicals can induce immune activation. This was followed by Ian White from St John's Institute of Dermatology, St Thomas' Hospital, who provided a detailed analysis of the genetic factors, polysensitisation, and complexities inherent in contact allergy.

In her own presentation, Charlotte Menné Bonefeld highlighted the pivotal role of T cells in allergic contact dermatitis, demonstrating how adaptive immune responses in the skin can shape clinical outcomes. Thomas Rustemeyer from the VU University Medical Center then offered valuable insights into the balance between tolerance and anti-inflammatory mechanisms in allergic contact dermatitis.

Luca Stingeni from the University of Perugia discussed delayed hypersensitivity to corticosteroids, addressing both topical and systemic aspects of this response. Suzana Ljubojevic Hadzavdic from the University Hospital Center Zagreb, University of Zagreb School of Medicine, subsequently examined contact hypersensitivity in patients with other skin diseases, underscoring the interconnected nature of dermatological conditions. The final presentation by Olivier Aerts from University Hospital Antwerp and the University of Antwerp's Research Group in Immunology offered a forward-looking perspective on potential new treatments for allergic contact dermatitis.

The sessions were chaired by Jeanne Duus Johansen (National Allergy Research Centre, Department of Skin and Allergy, Gentofte Hospital) and Ana Maria Giménez-Arnau (Department of Dermatology, Universitat Pompeu Fabra), ensuring a dynamic exchange of ideas.

The symposium concluded on a high note, with closing remarks that reinforced the value of interdisciplinary dialogue and the importance of continuing collaborative efforts to advance our understanding of chemical-induced immune reactions in the skin. Overall, the event provided a stimulating platform for knowledge exchange and set the stage for future innovations in the field.

VISIT FROM MD
PHD STUDENT HERIELLY MSUYA

In 2024, the T Cell Biology and Skin Inflammation group, led by Carsten Geisler and Charlotte Menné Bonefeld, initiated a collaboration with the Regional Dermatology Training Centre, Kilimanjaro Christian Medical Centre in Moshi, Tanzania. A part of this collaboration is the project *"Prevalence and Immunological Phenotype of Allergic Contact Dermatitis (ACD) to Common Contact Allergens and of Cutaneous T Cell Lymphoma (CTCL) in Tanzania"* with dermatologist and MD Herielly Msuya who holds a PhD grant from SIC.

As part of his PhD studies, Herielly Msuya visited the group, where he was introduced to key laboratory techniques used to study skin immunology. During his eight-week stay in Denmark, he was furthermore introduced to patch testing and consumer safety practices related to contact allergens at the National Allergy Research Centre, Department of Dermatology and Allergy. This training was conducted under the supervision of Professor Jeanne Duus Johansen and leading physician Claus Zachariae.

HANDS-ON COURSE FOR FUTURE SCIENTISTS
GEFION GYMNASIUM

In 2024, SIC hosted its fourth two-day introductory course in skin immunology for biotech students from Gefion Gymnasium. Organised by Professor Charlotte Menné Bonefeld with support from her research group, the course provided students with practical laboratory experience, offering insight into selected techniques and equipment used in SIC's daily research activities.

The initiative reflects SIC's commitment to engaging the next generation of scientists and supporting science education at all levels. Each year, the course demonstrates how hands-on experience can significantly enhance students' understanding and interest in scientific research – highlighting the educational value of incorporating practical exercises into teaching.


HELiN

PHD PRESENTATION

Investigating the role of stromal cells as environmental sensors regulating intestinal immune homeostasis and disease

Christian Ashworth - PhD Student

The intestinal barrier is continuously exposed to trillions of microorganisms collectively known as the intestinal microbiota. The host immune system must maintain a careful balance, defending against pathogenic threats while simultaneously tolerating beneficial commensal microbes. Disruption of this equilibrium can have severe health consequences, contributing for example to the initiation and maintenance of inflammatory bowel disease (IBD); a chronic inflammatory intestinal disease characterized by a dysregulated immune response to the commensal microbiota.

The majority of immune cells orchestrating intestinal immune responses are situated within the lamina propria (LP), a connective tissue layer directly underlying the intestinal epithelial lining. The LP contains a large number and variety of specialized immune cells, including antibody producing plasma cells, and cytokine producing T cells, essential for regulating local immune responses. Immune cells within the LP are located within a complex network of tissue resident structural cells, collectively termed mesenchymal stromal cells (MSCs), including fibroblasts, smooth muscle cells and pericytes. While traditionally recognized for providing structural support of tissues, emerging evidence indicates that fibroblasts play crucial roles in immune regulation. Consistent with this, the human and mouse LP contains several distinct fibroblast subsets each of which expressing distinct arrays of environmental and bacterial sensors as well as surface and secreted molecules involved in immune cell recruitment, maintenance, and function. Nevertheless, the importance that fibroblast expression of these potential immune modulatory molecules on intestinal homeostasis and inflammation remains largely unclear

My PhD project broadly aims to assess the diversity and immune modulatory expression profile of intestinal LP fibroblasts in health and inflammation. In preliminary data we have found that subsets of human and murine intestinal LP fibroblasts express the ligand-dependent transcription factor aryl hydrocarbon receptor (AHR), an evolutionarily conserved environmental sensor that responds to dietary and microbial metabolites. A major focus of my project is thus to determine the role of AHR in fibroblasts on intestinal homeostasis and disease

To understand the significance of AHR in intestinal fibroblasts, I will utilize transgenic animal models with a selectively deletion of Ahr in intestinal fibroblasts. Intestinal immune, MSC and epithelial cell development will be examined in these mice from birth until adulthood to determine AHRs role in homeostasis. In addition, animals will be challenged with dextran sodium sulfate (DSS) to induce epithelial damage or infected with citrobacter rodentium to determine the importance of fibroblast expression of AHR in intestinal inflammation and infection. For each of these models I will make use of several in house state-of-the-art-methods including high-dimensional flow cytometry, single-cell RNA sequencing, confocal laser microscopy, and epithelial organoid/fibroblast co-culture systems. Ultimately, my goal is to provide mechanistic insights into how fibroblast-expressed AHR influences intestinal health and disease with potential therapeutic relevance for IBD.

Javiera Alvarez - PhD Student

Deciphering the immune landscape of Sinonasal Squamous Cell Carcinoma

Sinonasal Squamous Cell Carcinoma (SNSCC) is a rare and aggressive malignancy that often presents at an advanced stage and is associated with poor prognosis and limited treatment options. Unlike other head and neck cancers, SNSCC has not been extensively characterized and its immune landscape remains largely unexplored, leaving critical gaps in our understanding of its tumor microenvironment. Given its origin in the nasal and sinus cavities – tissues that serve as the first line of defense against environmental pathogens and inhaled particulate matter – it is crucial to determine whether this tumor is immunogenic, how immune cells shape its progression and whether immunotherapeutic strategies could be effective.

My research uses single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics to generate a comprehensive profile of SNSCC's immune landscape. I aim to define the cellular composition of these tumors, focusing on the diversity and distribution of immune cell populations. By mapping immune-epithelial-stromal cell interactions within the tumor, we seek to uncover potential immune niches that may contribute to tumor persistence or immune evasion.

A major focus of this study is the characterization of tumor-infiltrating T cells. Preliminary analyses suggest a substantial presence of regulatory T cells (Tregs) in SNSCC, a feature that distinguishes it from other malignancies of the head and neck region. The transcriptional profile of these T cells, along with their spatial distribution and potential functional states, ranging from cytotoxic and memory phenotypes to exhaustion, will be explored in depth. Additionally, we are investigating whether clonally expanded T cell populations are present and how they interact with other immune and non-immune cells. In vitro experiments will further assess the functional capacity of these clones and explore whether their fate is preserved when cultured with tumor-derived factors.

By integrating high-resolution transcriptomic and spatial data, I hope to provide a detailed map of SNSCC's immune landscape. This will help to elucidate key cellular interactions within the tumor microenvironment and shed light on whether patients with SNSCC would benefit from immune therapies.

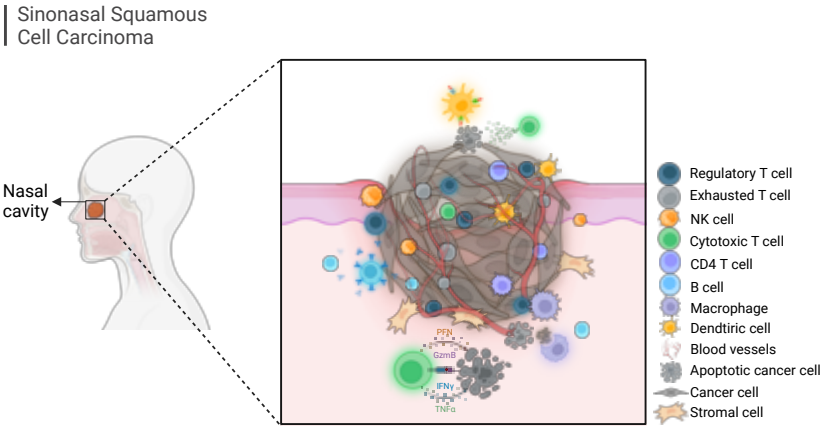


Figure: Schematic representation of the tumor location in SNSCC, highlighting key cellular components and interactions within the tumor microenvironment (TME). SNSCC exhibits a heterogeneous composition, including macrophages, stromal cells, dendritic cells, and tumor-infiltrating lymphocytes (TILs). In addition to cellular components, the TME also comprises non-cellular elements such as the extracellular matrix, which provides structural support, and signaling molecules that regulate cell-cell interactions within the TME. Made with Biorender.com.

PHD PRESENTATION

Characterization of T cells in the skin of healthy humans and patients with allergic contact dermatitis

Julie Weber Friis - PhD Student

The skin is the largest organ of the body, and it protects us against harmful events caused by sunlight, pathogens, chemicals, allergens, and so on. This protection is provided by a complex collaboration between immune and epithelial cells. My PhD project explores how the cellular composition of the skin varies depending on anatomical location and age, with a special focus on T cells. Additionally, I investigate whether there are any immunological differences between white skin and skin of colour.

In the second part of my study, I investigated whether different contact allergens induce different immune responses in patients with allergic contact dermatitis (ACD).

The project is performed in collaboration with Professors Lone Skov and Jeanne Duus Johansen and PhD student Mie Sonne Goldeman at the Department of Dermatology and Allergy, Copenhagen University Hospital - Herlev and Gentofte, and with MD, PhD student Herielly Msuya at the Regional Dermatology Training Centre, Kilimanjaro Christian Medical Centre in Moshi, Tanzania.

To investigate skin composition across age and anatomical sites, we recruited healthy donors in two age groups (18-60 and >60 years of age) and took skin punch biopsies from three different body sites. Each biopsy was split into epidermis and dermis, and cells were isolated and sorted, favoring the T cells. The sorted cells from the biopsies were used for ECCITE-seq (Expanded CRISPR-compatible Cellular Indexing of Transcriptomes and Epitopes by Sequencing), which provides a picture of the cellular composition in the different sites and across age groups.

The new fixation protocol from 10X Genomics, FLEX, has enabled us to investigate skin of colour in Tanzania. Through the Regional Dermatology Training Centre, we recruited healthy individuals in the same two age groups as before and took skin punch biopsies from a single body site. Cells were isolated from the whole biopsy, fixed, and transported to Denmark for further processing, including cell sorting, favouring the T cells, and sequencing. This part of the study will add to the knowledge of how the cellular composition is affected by skin colour.

Additionally, we included people with albinism, a genetic condition more prevalent in the Kilimanjaro region than in many other parts of the world. Due to Tanzania's climate, people with albinism face a high incidence of skin cancer and continue to experience cultural stigma. A deeper understanding of their healthy skin composition may help support future health interventions.

Furthermore, for the second part of my PhD, we have analysed biopsies from patch tests from patients allergic to HEMA, MI, and PPD, and performed single-cell RNA sequencing (scRNA-seq) on the purified cells. We recruited allergic patients, conducted patch testing, and collected skin punch biopsies 24 hours after the second patch application, allowing us to study the immune response at the site of an active allergic reaction.

With this PhD project, I aim to expand the knowledge of immune cells in the skin across age, anatomical location, and skin type, as well as their role in ACD.

Amanda Kvist-Hansen - BRIDGE Fellowship

Systemic inflammation in psoriasis – platelets, neutrophils, and their interactions

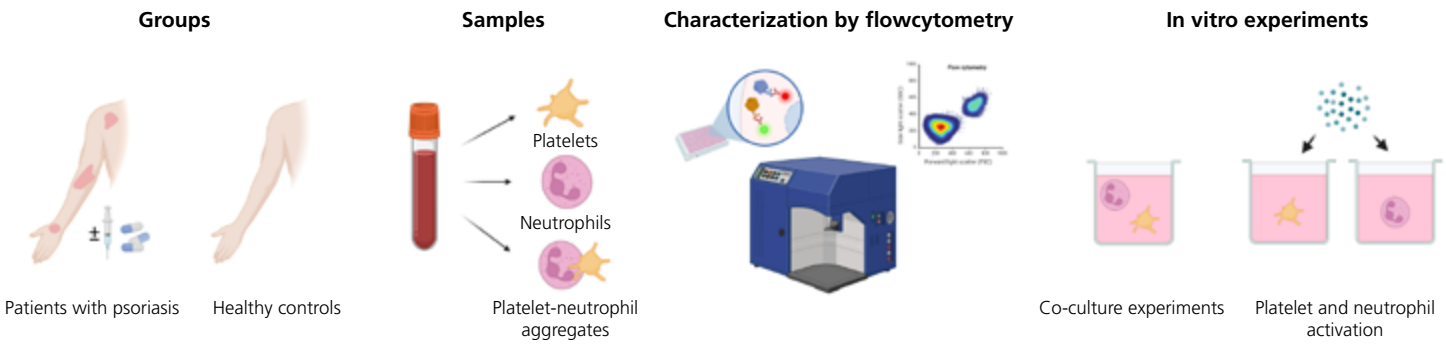
Psoriasis is a common chronic inflammatory skin disease with systemic implications, including an increased risk of cardiometabolic diseases. Although the main symptom of the disease is inflamed and scaly skin lesions, the patients also have low-grade systemic inflammation, evident by increased levels of inflammatory cells and cytokines in the blood. Low-grade systemic inflammation is considered an important contributing factor for both cardiovascular disease and psoriasis, but what exactly drives low-grade systemic inflammation in psoriasis and how it is affected by psoriasis treatment is not completely understood.

Skin inflammation in psoriasis is known to be driven by T helper 17 cells and the interleukin 23/17 pathway, and psoriasis therapies targeting these inflammatory mechanisms are highly effective in resolving skin inflammation. However, innate immune mechanisms are also likely to contribute to the inflammatory response in psoriasis. Interestingly, innate immune cells such as neutrophils and platelets are present in excessive numbers in psoriatic skin, and in the blood these cells are reported to exhibit increased activation. Furthermore, a disrupted balance between circulating adaptive and innate immune cells, measured by biomarkers such as the neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio, have been reported in patients with psoriasis. These findings suggest that innate immune mechanisms could be important for low-grade systemic inflammation in psoriasis. Therefore, the role of neutrophils and platelets in low-grade systemic inflammation in psoriasis and how treatment affects these cells needs to be better understood.

The aims of the project are to characterise circulating platelets and neutrophils in psoriasis and to investigate their interactions and response to psoriasis treatment. Blood samples will be collected from patients with and without systemic psoriasis treatment and healthy individuals. The cells and their interactions will be characterised by flow cytometry and further investigated by in vitro stimulation and cell co-culture experiments.

This project will hopefully lead to a better understanding of how innate immune mechanisms contribute to low-grade systemic inflammation in psoriasis. By exploring these mechanisms, the project may help identify new biomarkers that can improve the management and treatment of low-grade systemic inflammation in patients with psoriasis thereby potentially reducing their cardiovascular risk.

Figure: Experimental setup



Outreach and communication

SIC researchers actively engage in outreach and communication to share their findings with diverse audiences, including the scientific community, healthcare professionals, policymakers, industry, and the general public.

In 2024, SIC expanded its presence across various media platforms, contributing to scientific articles, interviews, and press releases. Researchers participated in podcasts and films to communicate complex immunological topics in an accessible way, while public lectures and events provided opportunities for direct engagement. Digital platforms, including social media, further amplified the impact of these efforts.

The following highlights key outreach and communication activities from 2024.

MEDIA AND INTERVIEWS

DAGENS MEDICIN
A thematic issue of Dagens Medicin featured research by Niels Ødum in the article "Gule stafylokokker gør T-celle lymfom i huden behandlingsresistent". The piece explored how Staphylococcus aureus influences treatment resistance in T-cell lymphoma. The publication reaches a broad audience, including specialists, hospital staff, and primary healthcare providers.

SCIENCE NEWS
Niels Ødum was interviewed for Science News, the Novo Nordisk Foundation's scientific newsletter, where he discussed how Staphylococcus enterotoxins induce resistance in cancer cells. The newsletter presents scientific discoveries in an accessible format for a general science audience.

DANISH CANCER SOCIETY
The Danish Cancer Society's annual research report featured an article on skin lymphoma research by Niels Ødum, titled "Research Offers Hope for New Treatments for Skin Lymphoma". The report reaches researchers, patient organisations, and the general public interested in cancer treatment and prevention.

The Danish Cancer Society also highlighted Niels Ødum's work in their newsletter article "Bacteria Can Inhibit the Effectiveness of Cancer Medicine". This publication reaches a wide readership with an interest in cancer research and treatment developments.

UNIVERSITY OF COPENHAGEN PRESS RELEASE
A University of Copenhagen press release, "Germs Can Offset the Effect of Cancer Therapy", featured Niels Ødum's research. The article was made available in both English and Danish to ensure broad accessibility.

DAGENS ETC
Liv Eidsmo contributed to a discussion on healthcare for psoriasis in Sweden in an interview with Dagens ETC. The article provided insight into patient care and treatment strategies within the Swedish healthcare system.

EPSILOON MAGAZINE
Erik van Tilburg Bernardes contributed to an article on the fungal microbiome (mycobiome) for Epsiloon Magazine. He was among 88 international experts providing insights for the feature "Après le microbiote... voici le mycobiote!", published both online and in print.

PSORIASISTIDNINGEN
Albert Duvetorp was interviewed for Psoriasistidningen, the Swedish Psoriasis Patient Organisation's members' magazine. The article focused on his PSODEEP1 study, first presented at the EADV Amsterdam conference, and served as a platform to encourage patient participation in the upcoming PSODEEP2 study.

FILM AND PODCAST CONTRIBUTIONS

PODCAST SERIES ON IMMUNOLOGY

Several SIC researchers participated in T-time, a dedicated section in a podcast series hosted by dermatologist Iben Miller, which explores various aspects of immunology:

- Bill Agace contributed to an episode discussing the interplay between the gut, diet, microbiota, and the immune system, making complex immunological concepts accessible to the general public.
- Charlotte Menné Bonefeld has been actively involved in developing and supporting the podcast, contributing expertise on immunological memory.
- Jonathan Coquet participated in a segment discussing the role of T cells in inflammatory disorders.
- Mads Gyrd-Hansen contributed to T-time explaining about ubiquitin in inflammation and immunology.
- Lone Skov joined the main part of the podcast in an episode discussing psoriasis and diet.

DERMA-DERMA PODCAST

DERMA-DERMA is an eight-part podcast series focused on skin biology, diseases, and treatment. Distributed via social media, the series aims to raise awareness of skin health among younger audiences (15–22 years old).

The podcast is hosted by Karen Marie Groth from BeautyHero and serves as a platform for knowledge sharing on skin health and skin diseases, with regular contributions from SIC and ISIM researchers.

In 2024, SIC researchers Niels Ødum, Anders Boutrup Funch, Carsten Geisler, Charlotte Menné Bonefeld, and Anders Woetmann presented their research on the podcast.

The series will continue in 2025, with plans for live episodes during the annual summer event, Folkemødet.

UGESKRIFT FOR LÆGER

Lone Skov joined a podcast for a discussion on psoriasis, comorbidities, treatment, and its impact on patients.

WINE & SCIENCE

Martin Kongsbak-Wismann was invited to speak at Wine & Science, a popular public lecture series at the University of Copenhagen. His talk, *"Solens vitamin – kan D-vitamin hjælpe vores immunforsvar?"* (The Sun's Vitamin – Can Vitamin D Help Our Immune Defence?), attracted a full audience of 450 participants and engaged the public in discussions on the role of Vitamin D in immune function.

FOLKEMØDET 2024

Rune Kjærsgaard Andersen participated in Folkemødet 2024, leading a session titled *"The Great Patient Roulette: The Fight Against Hidradenitis Suppurativa (HS)"*. The event was divided into two segments:

- A personal testimony from a 22-year-old patient living with HS, shedding light on the daily struggles and misconceptions surrounding the disease.
- A scientific explanation of HS, debunking myths such as the belief that it results from poor hygiene.
- A political debate on stigma, late diagnoses, and comorbidities, where participants engaged in a "patient roulette" exercise to understand the barriers to proper diagnosis and care.

The session is available for viewing on Sundhedstv.dk.

MIC TO MIC: MERGING SCIENCE AND MUSIC

Marina Ramírez Galera was an invited speaker at Mic to Mic: Where Music Meets Science, an event designed to bridge research and society. Marina presented her research in an informal setting and engaged the audience by performing songs on her guitar, illustrating the creative connection between science and music.

SIC SEMINARS

The SIC Seminars, organised by SIC's own young researchers at the Mærsk Tower, continue to serve as a vibrant forum attracting researchers not only from the Department of Immunology and Microbiology (ISIM), but also from other departments at SUND, as well as universities and clinics across Denmark. In 2024, SIC hosted seven seminars featuring international speakers, including talks held in connection with PhD defences and visits by professors to other SIC members. The series remains a valuable platform for scientific exchange, with more engaging speakers already planned for the coming year.

SEMINARS ORGANISED BY SIC RESEARCHERS AND HOSTED AT THE MÆRSK TOWER

Dr. Charlotte Odendall, King's College London
Interferon: Tug of War between Host and Pathogen.

Professor Philipp Henneke, University of Freiburg
Development of innate immunity in barrier tissues

Professor Thomas Korn
An unexpected role of B cells in neuromyelitis optica

Professor Georg Gasteiger, Würzburg Institute of Systems Immunology
Local players in immunity: development, niches and functions of tissue-resident innate and adaptive lymphocytes"

Dr. Stephen McSorley, University of California Davis
Understanding protective memory responses to Salmonella and Chlamydia infection

Fern Koay, University of Melbourne, Australia
Unconventional, innate-like T cells: development, homeostasis and regulation

Professor Dr. Dr. Jürgen C. Becker, Universität Duisburg-Essen Biologische Fakultät, Germany
Merkel cell carcinoma: insights from an immunogenic tumor

Organising committee of the SIC seminars

- Jonathan Coquet
- Rasmus Agerholm-Nielsen
- Chris Kedong Wang
- Urs Michael Mörbe
- Ekaterina Zhuravleva
- Hannah Paludan

Funding

SIC was awarded DKK 400 million by the LEO Foundation for Center operations in 2019-2028, distributed on a base grant of DKK 250 million and a pool for add-on grants of DKK 150 million. The turnover from the base grant totalled DKK 27.3 million, and the turnover from the add-on grants totalled DKK 14.4 million in 2024. Also, SIC obtained a total of DKK 23.4 million in new funding from 11 external research grants.

External research grants awarded in 2024

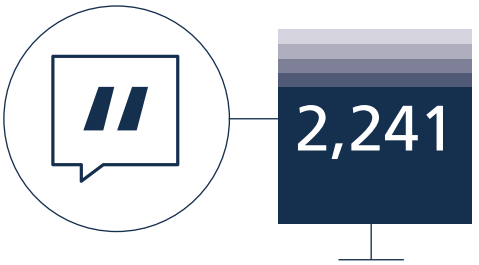
Funder	Recipient	Title	Amount in DKK
Stiftelsen Psoriasisfonden	**Albert Duvetorp**	PSODEEP2 (2nd payment for this project)	**68,000** (SEK 100,000)
Dyssegårds Fond	**Anders Boutrup Funch**	Role of B cells in allergic contact dermatitis and in tolerance to contact allergens	**45,000**
EU PARC	**Charlotte Menné Bonefeld**	New Approach Methods in the risk assessment of skin sensitizing mixtures	**1,001,000 (EUR 135,900)**
Danish Cancer Society (Kræftens Bekæmpelse)	**Chella Krishna Vadivel**	Young Talented Cancer Researcher - Personalized treatment targeting malignant T cells	**1,550,000**
EMBO (European Molecular Biology Organization)	**Erik van Tilburg Bernardes**	Deciphering the role of microbiome-fibroblast crosstalk in intestinal immune development, homeostasis and inflammation	**1,337,000** (EUR 180,000)
Aase & Ejnar Danielsens fond	**Martin Kongsbak-Wismann**	Kan bakterier undvige vores immunforsvar ved at destabilisere vitamin D receptoren?	**187,000**
Kræftens Bekæmpelse	**Niels Ødum**	Bakterier gør kræftceller resistente overfor lægemidler gennem samspil med de omgivende celler i T celle lymfom i huden.	**3,000,000**
BRIDGE: Translational Excellence Programme - Novo Nordic Foundation - University of Copenhagen BRIDGE Program	**Niels Ødum**	Systemic inflammation in psoriasis platelets, neutrophils, and their interactions	**2,000,000**
BRIDGE: Translational Excellence Programme - Novo Nordic Foundation - University of Copenhagen BRIDGE Program	**Niels Ødum**	T-cell metabolic fitness and clinical outcome after allogeneic stem cell transplantation	**2,000,000**
Dr. Abildgaard Fellowship, LEO Foundation	**Wenning Zheng**	Uncoupling the contribution of systemic and site-specific immunity in inflammatory skin disorders	**12,000,000**
Novo Nordisk Foundation	**William Agace**	Sponsorship International Conference of Mucosal Immunology	**250,000**

Scientific output

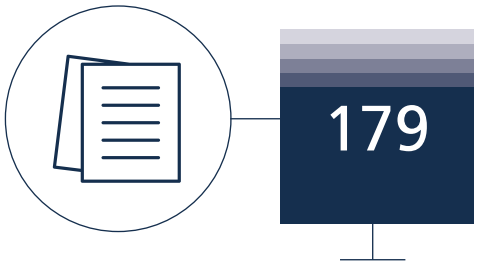
SIC and BIOSKIN researchers authored 50 publications in peer-reviewed journals in 2024.

SIC publications 2019-2024

2019	2020	2021	2022	2023	**2024**
25	19	34	22	34	**45**

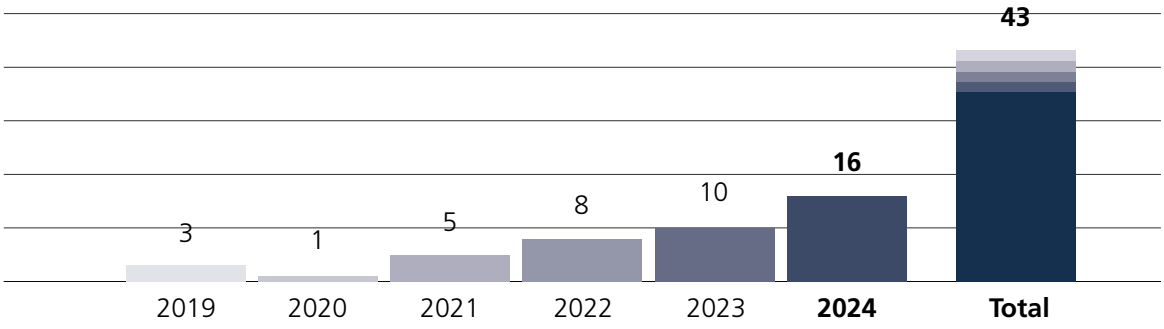


Total citations from SIC Group Leaders in 2024



Total SIC publications

Number of publications · impact factor >10



Publications

Publications are listed in alphabetical order by article name. Journals are in bold.

A genome-wide association meta-analysis links hidradenitis suppurativa to common and rare sequence variants causing disruption of the Notch and Wnt/β-catenin signaling pathways.
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Selected publications from BIOSKIN 2024

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