

Annual Activity Report 2022

LEO Foundation
Skin Immunology
Research Center



UNIVERSITY OF
COPENHAGEN

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Introduction

With a unique focus on inflammatory skin diseases and a 10-year perspective in research and educational development, the LEO Foundation Skin Immunology Research Center unravels key questions on some of the world's most widespread skin conditions.

The skin is our largest organ and the number of skin diseases is staggering, with more than 3,000 known diseases. Some are quite manageable, but remain incurable and unexplained, whereas others are serious and even life-threatening.

In the US, skin disease impacts one in four persons in a given year and, in Denmark alone, up to 20% of school children suffer from atopic dermatitis.

As such, skin diseases have a huge impact on individual quality of life as well as on society as a whole.

The field of dermatology – the branch of medicine dealing with the skin, its structure, functions and diseases – draws on research from immunology, pathology, microbiology, neurology and oncology.

Our knowledge of skin diseases has accelerated over the past decade, and the pathophysiological basis of many of the diseases is gradually being elucidated. Conceptualising the skin as an immunological organ has proven very fruitful, and discoveries within immunology have paved the way for new treatments.

Despite significant progress, the pace of innovation is, however, not sufficiently high, and new treatments are slow to reach the patients. To boost our knowledge level, we established the LEO Foundation Skin Immunology Research Center (SIC) 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 inflammatory skin diseases, including psoriasis, atopic and contact dermatitis and cutaneous T cell lymphoma (the latter as a

model disease), which are all characterised by a strong immunological component. SIC's aim is to integrate, bridge and advance basic and clinical scientific approaches to skin disease and develop, cultivate and nurture future scientists and leaders in the field, and concurrently increase the knowledge and awareness of skin and skin diseases among medical professionals, patients as well as the public. Our aim is to grow into a beacon for skin research in Denmark with a worldwide impact.

MISSION

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

VISION

The LEO Foundation Skin Immunology Center will become a world-leading center for research and education in skin and skin diseases.

DISEASE FOCUS

- ‡ Psoriasis
- ‡ Atopic dermatitis
- ‡ Contact dermatitis
- ‡ T cell lymphoma as a model

KEY RESEARCH THEMES

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

Director's corner



Group leader and Professor Liv Eidsmo is Executive Director of SIC.

My most memorable moment at SIC in 2022 was when I caught John, one of our postdocs, proudly showing a picture of data from the microscopy facility on his phone to his peers over lunch. Students and postdocs from different groups in our center leaned into the picture and an intense discussion followed on how to interpret this new data. A few months back, John had introduced an obstacle in his project at our biweekly lunch seminar. The feedback from the SIC community gave him the necessary tools and insights to solve the problem. John's shared excitement over raw data encapsulated the very heart of my vision for SIC; innovative science made better through a synergistic mindset across the center.

SIC aims for excellence in research, clinical translation of our findings, training the next generation of skin immunologists and outreach activities to patients and the general public. During the past year, our internal scientific advisory board and our first external review highlighted the breath of robust and creative projects at SIC. The first center-wide blue-sky research project was launched by Mads Gyrd-Hansen where post-translational protein modifications in healthy and diseased skin is

investigated from our different perspectives. After a thorough recruitment process, we welcomed Associate Professor Jonathan Coquet and his group Allergic Immunology. With Jonathan, we gain cutting edge expertise in allergic and atopic inflammation in barrier tissues, with projects bridging animal models and human tissues. Jonathan has a vibrant scientific persona and brings his worldwide network to the SIC community.

Among the many training opportunities SIC offers, the second Summer School at Hornbæk, initiated by Charlotte Menné Bonefeld, was again a highlight. Expanding our clinical and translational integration, Lone Skov and Jeanne Duus Johansen started recruiting patients to the BIOSKIN biobank. BIOSKIN will provide important information on the disease trajectories of psoriasis, atopic and allergic contact dermatitis as well as clinical material to the discovery-based projects run in the laboratories at SIC.

The SIC community had another active year in outreach activities, including a night on "collaboration and science" for dermatologists the night before the Nordic Dermatology Conference started in Copenhagen, Anders Woetmann explained skin regeneration to the general public in the Bloom festival, Niels Ødum and BIOSKIN interacts closely with patient representatives, and I participated in "Tour de Health" with decision makers in health care from all over the world.

Another busy year has passed, and SIC is moving from the establishment phase to consolidating activities. Next year we hope to identify a sixth scientist to join the SIC faculty, Springtime School is just around the corner and the technical platform will expand with a multiphoton microscope. But most importantly, SIC will continue to offer a platform to explore the frontiers of skin immunology together with our next generation of skin immunologists.

Report from the Dean



Bente Merete Stallknecht assumed the position as Dean of the Faculty of Health and Medical Sciences, University of Copenhagen in May 2022 succeeding Ulla Wewer.

My first encounter with the LEO Foundation Skin Immunology Research Center (SIC), after stepping into my new role as Dean, was during SIC's Scientific Advisory Board review where I was thrilled to learn about all the highlighted initiatives and activities in SIC. The center rests on four key pillars in our passion to make a difference for people with skin diseases globally: excellence in research, training the next generation of skin immunologists, clinical and translational integration of research activities and outreach to patients and the public.

Coming from the role of Prorector for Education, I was delighted to discover that SIC embraces all levels of education and training from high school students to fellowships, and also offers promising futures for researchers through career development in multiplex ways. Thus, playing multifarious educational strings, SIC both sustains the thriving of the current generation of top immunology researchers and ensures development of the next-generation skin immunologists.

Alongside creating training opportunities, SIC aims to link basic and clinical research. Thus, the collaborative BIOSKIN program was initiated in 2021 with a DKK 40 million add-on grant from the LEO Foundation, and in 2022 this cooperation continued, further substantiating the bridging of basic science and clinical medicine.

The center proudly welcomed Associate Professor Jonathan Coquet as a new group leader, meaning that the center now consists of five growing and active basic research groups with flourishing scientific interaction at the headquarters on the 12th floor of the Mærsk Tower.

SIC continues to expand and consolidate their portfolio in all four key pillars creating scientific activity and paradigm-challenging results that spark and inspire as they share their findings with the world-wide scientific and clinical communities as well as the people we are here to ultimately help: the people with skin diseases.



New Group leader

In 2022, Jonathan Coquet joined as leader of a new group at the LEO Foundation Skin Immunology Research Center (SIC). Behind him are years of experience and knowledge from previous research on immunology, T cells, asthma, and allergies.

Jonathan Coquet's main research area is T cells and understanding allergies and asthma, but he has worked in various fields of immunology.

He grew up in Australia, where he also began his research career at the University of Melbourne and completed his PhD in 2008. Thereafter, he moved to Amsterdam and did a three-year postdoc at The Netherlands Cancer Institute. He then started applying his knowledge of T cells to allergic diseases during another postdoc at the University of Ghent in Belgium. In 2014, Jonathan joined the Karolinska Institute in Stockholm as an Assistant Professor.

As newly appointed Associate Professor he now leads a research group at SIC focusing on T cells and understanding how allergic diseases such as asthma and eczema develop.

Jonathan's primary research area at SIC will be to gain fundamental insights into eczema, which is typically an allergic disease. Unlike hay fever, where we typically know what is causing the allergic response (for instance grass or pollen), there are a lot of unknowns when it comes to the causes of eczema.

Jonathan presents his group "Allergic Inflammation" in more detail on pages 10-11.

The Scientific Advisory Board

The Scientific Advisory Board (SAB) provides guidance on scientific and strategic directions that support the center's international impact. The members of the SAB contribute with perspectives from Europe, the United States of America and Japan on discovery- and translational research in skin immunology, biobanks, imaging, genetics and community outreach. During two intense days in May 2022, the SAB provided valuable feedback on the visions, ongoing research and future plans in SIC, and engaged in scientific discussions with the group leaders, junior faculty and post docs.

The SAB highlighted that the new Executive Director's energy, enthusiasm, and clear vision for the future of SIC. The exciting scientific discussions in the center and in the accelerated expansion of the groups was highly appreciated by the SAB. In this context, the SAB was delighted to meet the two new group leaders, Mads Gyrd-Hansen, and Jonathan Coquet, who contributes with new areas of immunology and master a repertoire of cutting-edge technologies that complements the strong research performed by the original SIC members. The SAB furthermore expressed support to recruit an additional group leader.

The board members unanimously expressed their appreciation of the overall excellent scientific quality, the relevance of current scientific projects, the rapid progress made on new initiatives, and was also impressed to see that its earlier recommendations to shoulder a publicity campaign to raise international awareness of SIC had been implemented. In particular, the increasingly popular Summer/Springtime School was highlighted. The SAB praised the clinical faculty for their excellent establishment of the BIOSKIN program during challenging pandemic times and suggested looking into whether the BIOSKIN program could expand the disease scope to shed light on rare skin diseases.

The board encouraged SIC to continue advancing the scientific network of post docs and students via a wide span of collaborations and exchanges to and from the center. Furthermore, the board supported the plan to fund PhD studies initiated in a collaboration with two or more SIC research groups. To continue to build an open scientific environment in a changing culture, the SAB suggested presentations of early-stage ideas/projects and to further engage junior researchers in asking questions during seminars and small and larger meetings with or without the principal investigators. This will train the next generation to emphasize the crucial acquired skill of being able to ask others for technical and conceptual help.

The board supported SIC in taking scientifically greater risks for greater rewards when tackling the fundamental open questions in skin immunology and underlined that this may be facilitated by continuing to reinforce plentiful opportunities for the groups to openly interact, brainstorm and provide seed funding for promising synergistic projects. Lastly, the SAB also expressed a firm belief that the strong focus on applying fundamental basic immunological methods and knowledge to skin diseases, as well as on the translation of this knowledge of treatments, will continue to contribute to important scientific progress as well as improve the life of patients with skin diseases in many decades to come.

THE SAB CONSISTS OF

- Tomas Mustelin, University of Washington, USA (Chair)
- Riitta Lahesmaa, University of Turku, Finland
- Muzlifah Haniffa, Newcastle University, England
- Olle Kämpe, Karolinska Institutet, Sweden
- Mübeccel Akdis, University of Zurich, Switzerland
- Kenji Kabashima, Kyoto University, Japan
- Rachael Clark (not present), Harvard Medical School, USA
- Immo Prinz (not present), University Medical Center Hamburg-Eppendorf, Germany

Organisation and governance

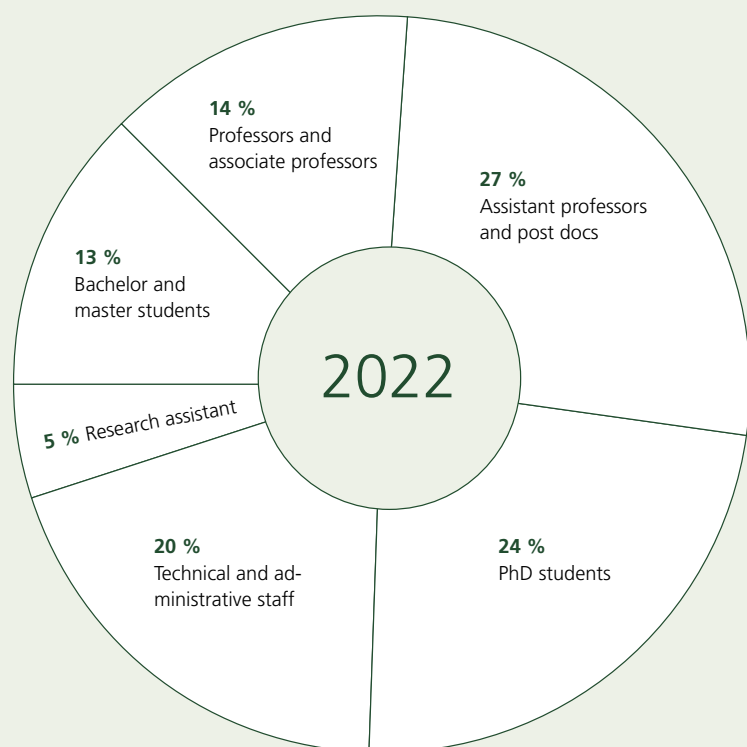
SIC is a separate organisational entity embedded in the Department of Immunology and Microbiology (ISIM) at the Faculty of Health and Medical Sciences at the University of Copenhagen. SIC's basic research groups are based at the Mærsk Tower headquarters in the heart of Copenhagen. Scientific collaborations are in place across the Faculty, national and international clinical research units and the life science industry, stimulating ample opportunities for interdisciplinary synergistic plexus.

Staff composition

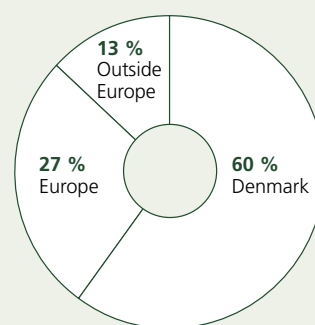
By the end of 2022, a total of 69 staff members and students of 15 different nationalities were engaged in SIC's six basic research groups. The compositional staff data presented here include visiting guest researchers, PhD students to whom SIC researchers provide main supervision and bachelor and master's students (students conducting their thesis work or completing exchange stays in SIC's laboratories).

The core members

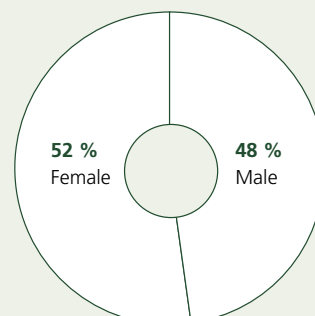
After the addition of the new research group 'Allergic Inflammation' in 2022, SIC has six core groups: Basic Research Group Leaders and Professors Liv Eidsmo, Carsten Geisler (with Charlotte Menné Bonefeld), Anders Woetmann (with Niels Ødum) and Mads Gyrd-Hansen, clinical Professor at Herlev and Gentofte Hospital, Jeanne Duus Johansen (with Lone Skov) and Associate Professor Jonathan Coquet. The core members make up the Center Steering Committee which proposes and implements strategic scientific



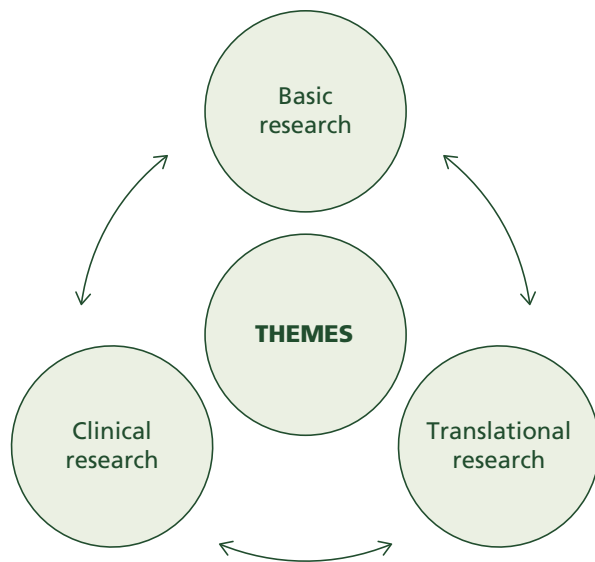
Distribution of staff and students by position



Nationalities of scientific staff and students



Gender distribution of scientific staff and students



THE TEAM SCIENCE CONCEPT

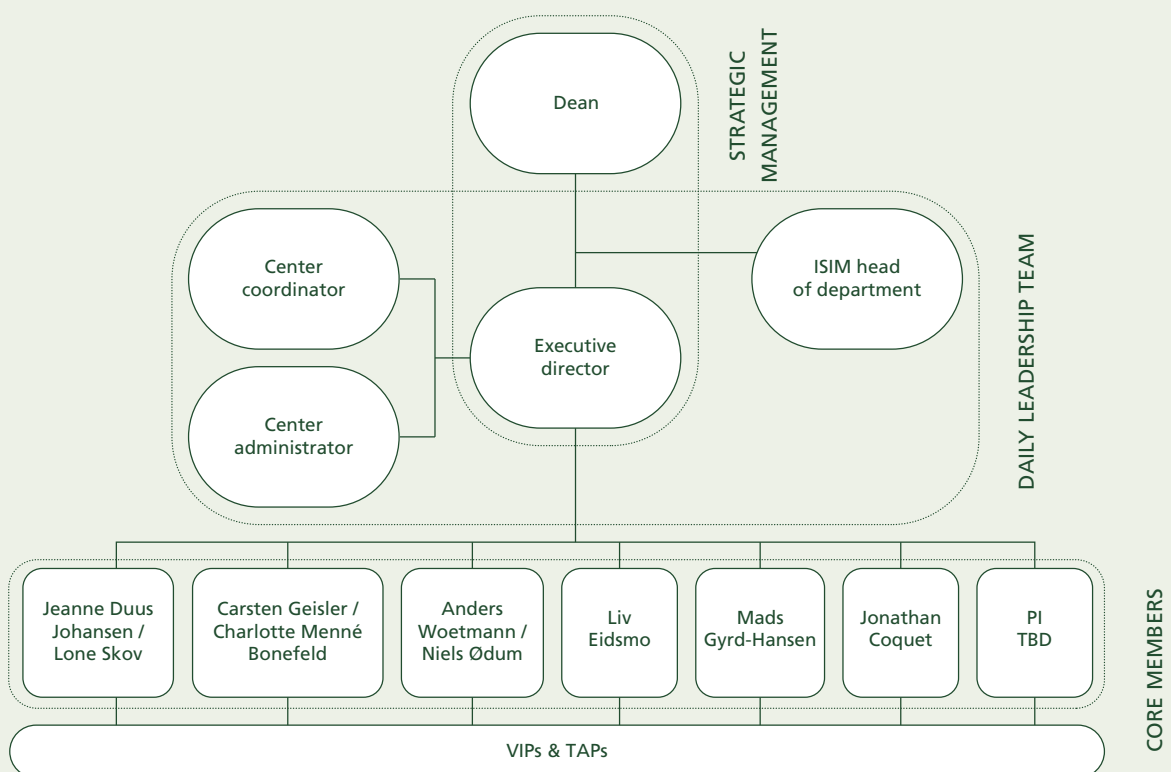
SIC investigates fundamental questions within skin biology and diseases in an interdisciplinary team of scientists with core competences and insights into basic, translational, and clinical skin-related research. We call this 'the Team Science Concept'.

initiatives. The group of core members constitutes the key framework behind the 'Team Science Concept'.

Management

SIC's Daily Leadership Team – consisting of Executive Director Liv Eidsmo, ISIM Head of Department Charlotte Menné Bonefeld, Center Administrator Nils Erik Samdal and Center Coordinator Bitten Dalsgaard (preceded by Hannah Paludan from 2023) – executes and oversees the center's day-to-day operations.

The Executive Director meets with Dean of the Faculty of Health and Medical Sciences, Bente Merete Stallknecht, on a regular basis to discuss and decide strategic matters related to the continuous development of SIC. Once a year Rector of the University of Copenhagen, Henrik C. Wegener, who is the grant holder of the SIC grant, aligns with the Center Management and the LEO Foundation on strategic progress and development. Once a year, Center management meets with Leo Foundation to present the current strategy and agenda.



Organisation and governance chart

Allergic Inflammation

The Allergic Inflammation Basic Research 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 Group Leader and Associate Professor Jonathan Coquet.

Over the last few years, the group has defined molecular processes by which T cells are activated and differentiate in response to allergens. To do this, we have used sensitive techniques, which are capable of analysing gene transcription in single cells and assays that measure the metabolic activity of allergy-causing T cells, called 'Th2' cells. These studies have shown that Th2 cells express many genes involved in the metabolism of fats, which they might acquire through our diets, or through their own production capacity. Th2 cells use these fats and lipids to become highly inflammatory and to cause allergic diseases such as asthma.

In 2022, the group has focused on an important paradigm in the field of allergy research: the notion that a 'dirty' environment may protect one from the development of allergies. Since the 1980s, it has been hypothesized that the striking rise in the incidence of allergies, firstly in developed countries, and now across the globe, may be due to the reduced exposure of humans to some microbes. Now, three decades later, it is largely agreed that this is an oversimplification of the original hypothesis. Nonetheless, intestinal microbial diversity has been shown to dampen inflammation and promote health outcomes, while some parasites (such as worms) similarly have been shown to reduce allergic pathologies. In collaboration with groups around Europe, our group has tested the impact of increased microbial diversity and supposedly beneficial worm infections on allergic immune responses.

Our results reveal widespread effects of microbial diversification on the immune system. Worms and microbially rich environments drive local and systemic T and B cell responses that have the potential to be both vigorous and anti-inflammatory in nature. Yet, allergens introduced into this system still clearly drive robust inflammatory responses, with very little signs of control coming from the enriched microbial milieu. Of interest, T cells in this particular environment respond in a non-classical manner to incoming allergens, by a mode typically referred to as 'T cell receptor-independent' mode, which is a non-specific mode of activation primarily associated with cells of the innate immune system. The question our group is currently puzzling over is whether this 'T cell receptor-independent' mode of activation is sufficient to drive allergy, or whether these cells have been reprogrammed and now act in less predictable ways.

Thus, our coming work will focus deeply on T and B cells of patients with eczema and asthma, to understand the quality of the cells driving allergy. Hence, moving into next year one of the questions at hand for our groups is: can we find evidence not only that these cells respond with this non-classical mode of action, but that they have acquired the ability to furthermore respond strangely and aggressively to typically non-inflammatory stimuli?



Associate Professor

// Jonathan Coquet

Postdoc

/ Egon Urgard

PhD student

/ Javiera Alvarez Moran

Research Assistant

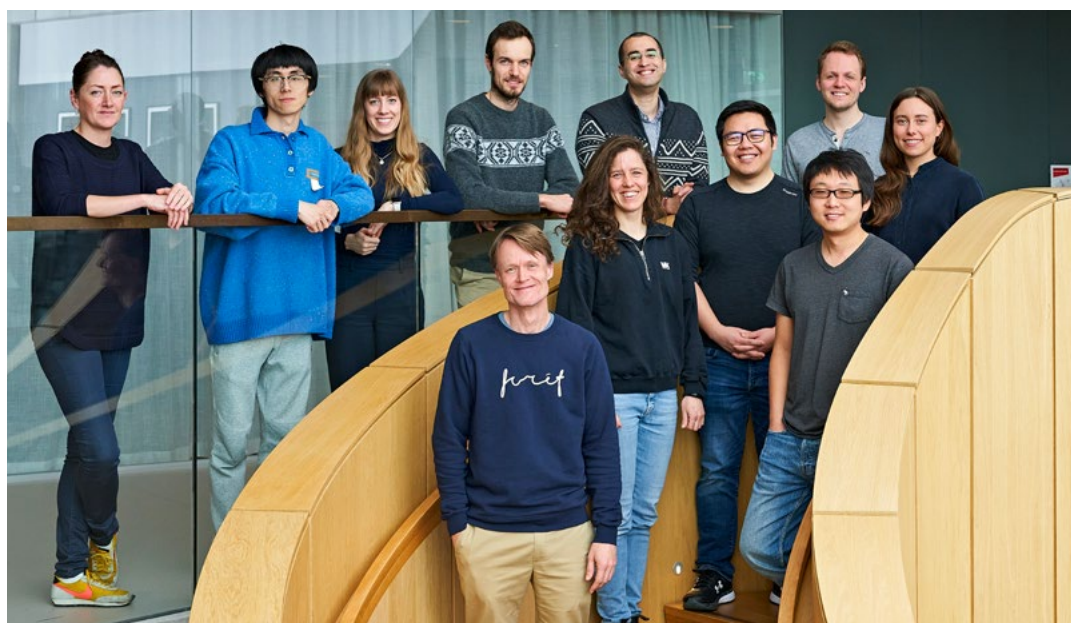
/ Alma Lindell



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. The group was established September 2020 with the recruitment of Professor Mads Gyrd-Hansen from the University of Oxford.

Our research has a particular focus on the ubiquitin system, which plays a central role in regulating inflammation and immune responses. The modification of proteins with ubiquitin, termed ubiquitination, is essential for signalling by immune receptors, where ubiquitin is assembled into polymeric ubiquitin chains by ubiquitin E3 ligases and are disassembled by deubiquitinases. These chains, depending on how they are assembled, alter the function, subcellular location, or stability of the modified protein. Lys48-linked ubiquitin chains cause proteasomal degradation of the modified protein whereas Lys63- and Met1-linked ubiquitin chains function as signalling scaffolds in pro-inflammatory signalling. Met1-linked ubiquitin chains are exclusively assembled by the E3 ligase LUBAC and have emerged as a central regulator of inflammation and immunity in animal models as well as in humans. Leveraging our investigations of fundamental regulatory mechanisms, we will explore how Met1-linked ubiquitin chains specifically affect immune responses and inflammation in the skin.

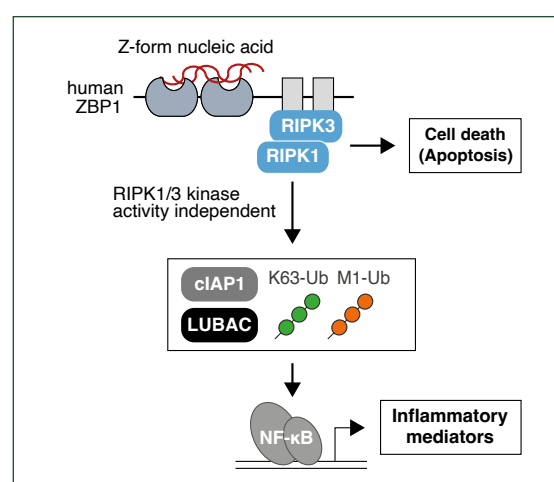


The group's primary objective in 2022 was to advance the newly initiated research projects at SIC, to finalise research projects that were initiated in the Oxford-based group, and to strengthen our molecular biology/proteomics capabilities through new staff recruitment. To this end, we have welcomed two new postdoctoral fellows; Biao Ma and Max Sauerland. Biao carried out his PhD studies in our group in Oxford and has now moved to SIC to explore the physiological role of a novel mechanism by which TNF receptor 1 availability is regulated through 'translational regulation' (the process of controlling the levels of protein synthesized from its messenger RNA). Max Sauerland joined the group in November 2022 to develop

mass spectrometry-based analyses of ubiquitin signalling during skin inflammation. The current group consists of an assistant professor (tenure track), a lab technician, four postdoctoral fellows, three PhD students, and one Erasmus student. In addition to the LEO Foundation group funding, the group is generously supported by external funding from the Novo Nordisk Foundation (NNF Young Investigator Award) and a competitive 3-year postdoctoral fellowship from the Lundbeck Foundation (awarded John Rizk).

The main focus of the projects in the group is to understand how regulation of LUBAC and Met1-linked ubiquitin chains influences the immune system under basal conditions and in the context of skin inflammation or other challenges such as bacterial infection. These projects rely on novel genetically-modified mouse models that have been transferred from the group at Oxford University to UCPH during 2021 and are now being extensively characterised in different experimental inflammation models. We have also initiated a PhD project where we aim to identify and characterise novel regulatory mechanisms of LUBAC by using mass spectroscopy-based proteomics available through the Proteomics Research Infrastructure (PRI) at SUND.

The research output from the group in 2022 was the article "Human ZBP1 induces cell death-independent inflammatory signaling via RIPK3 and RIPK1" published in EMBO Reports. In this study we reveal that the nucleic acid sensor ZBP1 has the capacity to instigate pro-inflammatory signaling and cytokine production in addition to its well-described role in triggering programmed cell death of virally infected cells. We provide evidence that this role of ZBP1 may contribute to cytokine secretion in response to SARS-CoV-2 infection. Building on this discovery, we have initiated a project to explore the role of ZBP1 signaling in keratinocytes and skin inflammation.



ZBP1 is a nucleic acid sensor that induces cell death via RIPK3. We describe a ZBP1-induced inflammatory signaling pathway that is independent of cell death and is mediated by non-degradative ubiquitin chains.

In 2022 the group has been engaged in the education at the department. Berthe K. Fiil and I have established a new PhD course on Mechanisms in Innate Immune Signalling which ran successfully for the first time in January 2022. Also, Berthe K. Fiil is part of the organising committee for the SIC Young Investigator Network and I participate as a mentor in the Postdoc Mentoring Programme at the faculty.

The focus areas for 2023 will be to advance the on-going research projects relating to the role of Met1-linked ubiquitin in immunology and skin inflammation and to continue to contribute to education in molecular mechanisms of inflammation and immunology.

Professor

/// Mads Gyrd-Hansen

Assistant Professors and Postdocs

/// Berthe Katrine Fiil
/ Chris Kedong Wang
/ John Rizk
/// Biao Ma
/ Max Sauerland

PhD students

/// Frederik Timmermann
// Malin Jessen
/// Wenxin Lyu

Erasmus+ student

/ Hanna Kulvicki

Lab manager

/// Majken Kjær

Skin Inflammation and Cancer

In the Skin Inflammation and Cancer Basic Research Group we work on elucidating the interplay between immune cells, skin cells and the skin microbiota to understand skin immunity and what mechanisms drive benign and malignant inflammatory skin disease progression. In addition, we are investigating if any of the identified mechanisms can be exploited as new therapeutic areas for inflammatory skin diseases.

In 2022, our group persevered our investigations on the characterisation of the role of T cells in both benign and malignant inflammatory skin diseases. A continuous special focus area of our research is to understand the role of metabolism and oxidative stress as a disease driver in the pathogenesis of cutaneous T cell lymphoma (CTCL). We hypothesise that expanded understanding of the complex interplay between changes in metabolism or level of oxidative stress and proliferation and survival of malignant T cells, will allow for identification of novel therapeutic targets for treatment of CTCL.

Furthermore, we expanded our work aimed at understanding the significance of changes in keratinocyte gene expression and function induced by cytokines derived from malignant T cells in CTCL. We focus on investigating how downregulation of proteins impact e.g.

tight junctions in keratinocytes resulting in an impairment, or loss of function of the skin barrier, and how this leads to an alteration of the cutaneous microbial composition, and subsequent aggravation of the disease. Results from these investigations have the potential to advance our understanding of the important role of crosstalk between malignant T cells and the stroma, and to discover novel targets for therapeutic approaches in CTCL.

In addition, we prevail working on clarifying the anti-inflammatory and immunoregulatory potential of adipose derived stem cells (ASCs) for treatment of benign inflammatory skin diseases. To this end, we have successfully set up and standardised the protocol to isolate and differentiate human ASCs, and we are now concentrating on unravelling the main immunosuppressive mechanism of ASCs, and

Professors

/ Anders Woetmann
/ Niels Feentved Ødum

Associate professor

/// Thorbjørn Krejsgaard

Assistant professor

/ Terkild B. Buus

Postdocs

// Emil MH Pallesen

/ Katrine Baumann

(BRIDGE Fellow)

/ Morten Orebro

Holmström

/ Pia Rude Nielsen

(BRIDGE Fellow)

PhD student

/ Chella Krishna Vadivel

/ Eileen Wedge

/ Gillian Dao

/ Hannah Jorinde Glöckner

/ Ines Lecoq Molinos

/ Katharina Wørzner

/ Klair Fjældstad

/// Lisa Harth

// Maria Gluud Grøndahl

/ María Teresa Martín

Monreal

/// Marina Ramírez Galera

/// Martin RJ Namini

/ Mia Aaboe Jørgensen

/// Shayne Lavondua Ford

Lab assistant

/ Mariana Bronze



additionally investigating how inter- and intra-donor variation could potentially influence the therapeutic effect of ASCs. We hypothesise that the immunosuppressive properties of ASCs could pave the way to utilizing them as a cell-based curative therapy for different skin diseases.

Finally, we continue to elucidate the interplay between cutaneous innate immunity and bacterial metabolites, which harbours immunomodulatory properties as well as advancing the investigations on the characterisation of the immunomodulatory role of encrypted peptides generated by proteolytic degradation of endogenous proteins in the skin. Together, human and microbial, proteins represent an unexplored potential source of encrypted peptides that can be released after proteolytic cleavage by either microbial or human proteases. We hypothesise that microbial metabolites, as well as encrypted peptides released by proteolytic degradation of cutaneous proteins, drive host-microbiota interplay by affecting cutaneous microbiota as well as host innate immune responses, thereby contributing to skin homeostasis. A deeper understanding of the role played by microbial/host crosstalk in modulation of inflammation and maintenance of skin homeostasis is expected to unlock the door

to novel therapeutic targets for treatment of inflammatory skin diseases.

We have achieved several important results in 2022. We have discovered how lipid metabolism driven by the expression of the enzyme fatty acid synthase (FASN) play an important role in the proliferation and survival of malignant T cells in CTCL. We have furthermore discovered how targeting the enzymatic activity of FASN in combination with inhibitors that block the feedback loop controlling FASN expression, results in effective suppression of malignant T cells. Moreover, in collaboration with associate professor Dr. Lise Mette Rahbek Gjerdrum we have successfully implemented novel methods for studying unusual T cell subsets with potential important roles in skin diseases and in different healthy tissue. Finally, together with collaborators we have made a series of important new discoveries including (1) identification of the microRNA profile in early-stage Mycosis Fungoides, (2) functional characterisation of several novel targets for cancer vaccines, and (3) how Omalizumab (a monoclonal anti-IgE-antibody) serum levels predict treatment outcomes in patients with chronic spontaneous urticaria.

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 Group Leader and Professor Charlotte Menné Bonefeld and Carsten Geisler.

In our group, we investigate several aspects of T cell biology in connection with the skin: 1) how different factors e.g. skin proteins, vitamins, cytokines and hormones affect T cell development, activation and differentiation and how this consecutively impact T cell responses in the skin; 2) the development and regulation of different subsets of epidermal T cells in both healthy and inflamed skin and 3) the immune response to contact allergens.

In 2022, the focus of our group has been on the role of CD4⁺ and CD8⁺ T cells and local versus global T cell memory in allergic contact dermatitis (ACD), on whether vaccine-induced neutralizing of IL-1 β might alleviate ACD and on how vitamin D affects immune responses in humans.

We have investigated the role of CD4⁺ and CD8⁺ T cells in the response to clinically relevant allergens and the differences between local and global memory responses to contact allergens. During the sensitization phase, contact allergen-specific memory T cells are formed. Two major forms of memory T cells are generated: Tissue-resident memory T cells and circulating memory T cells. Tissue-resident memory T cells localize in the skin area exposed to the allergen, whereas circulating memory T cells reside in the blood circulation from where they can be recruited to the skin upon re-exposure to the allergen. Whether these two subsets of memory T cells induce different challenge responses to contact allergens was unknown. As the first, we have shown that tissue-resident memory T cells induce a rapid inflammatory response mediated

Professors

/ Charlotte Menné Bonefeld
/ Carsten Geisler

Associate Professor

/ Martin Kongsbak-Wismann

Assistant Professors and Postdocs

/ Helen Vaher
/ Mandy Menzel
/// Mia Hamilton Jee
/// Anne-Sofie Østergaard Gadsbøll

Associate Professor (externally associated)

/ Beatrice Dyring-Andersen
/// Marianne Bengtson Løvendorf

PhD students

/ Anders Boutrup Funch
// Kelvin Yeung
/// Veronika Mraz
/ Fatima Abdul Hassan Al-Jaberi

Bachelor, Erasmus+ and Master students

/ Alexandra Seibel
/ Emilia Sæderup Lindeløv
/ Emma Uttrup Ewing
/ Leila Gharehdaghi
/ Louise Aagaard
/ Salome Marine Astree Havard-Guibert

Lab managers and technicians

/ Julie Weber Friis
/ Rebecca Kitt Davidson Lohmann



by a massive recruitment of neutrophils, which is not seen in memory responses mediated by circulating memory T cells (Funch et al., 2022).

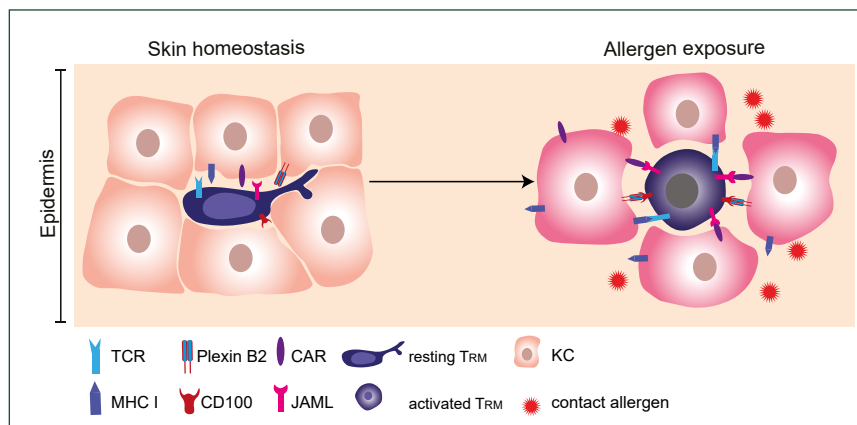
Furthermore, we have presented novel general insights into contact dermatitis (Johansen et al., 2022) and demonstrated the efficacy of a vaccine targeting IL-1 β for treatment of ACD (Goksøyr et al., 2022).

Additionally, we have extended our studies of a family with a new mutation in the DNA-binding region of the vitamin D receptor (VDR). We described the impaired ability of macrophages to produce cathelicidin (a protein with antimicrobial activity towards virus and bacteria including tuberculosis) in one of the family members, who in her adolescence suffered from extrapulmonary tuberculosis (Al-Jaberi et al., 2022). Moreover, we have studied the role of vitamin D on the expression of the glucagon-like peptide-1 receptor in various sub-types of T cells (Rode et al., 2022).

During the last years, we and others have shown that epidermal-resident memory T cells are rapidly activated after challenge with a specific antigen. Normally, it takes 1-3 days to re-activate memory T cells and it is therefore puzzling that epidermal-resident memory T cells can be re-activated within hours after challenge. It is known that different stress-molecules can be up-regulated on keratinocytes within hours after exposure to an antigen and/or danger signals. However, it is not known whether these stress-molecules are up-regulated in the response to contact allergens or whether they play a role in the rapid re-activation of epidermal-resident memory T cells. We have analyzed how contact allergens regulate the expression of the junctional adhesion molecule-like protein (JAML) and CD100 ligands CAR and plexin B2 on keratinocytes and the role of JAML and CD100 in the rapid flare-up responses seen after re-exposure to contact allergens in allergen-experienced skin. Our results indicate that contact allergens rapidly up-regulate CAR and plexin B2 on keratinocytes and that triggering of JAML and CD100 on the epidermal-resident

memory T cells play a central role in their rapid re-activation and the flare-up response.

Model for induction of stress-molecules on keratinocytes following stimulation with contact allergens and the role of stress-molecules in the activation of tissue-resident memory T cells.



Translational Skin Immunology

The translational skin immunology group strives to discover fundamental mechanisms of tissue immunology that can be targeted to eradicate localized disease memories and enable long-term remission for patients living with inflammatory skin diseases.

Despite the rapid expansion of systemic treatments for inflammatory such as psoriasis and atopic dermatitis, inflammatory skin diseases remain chronic and relapsing and continue to reduce the quality of life for patients at a high societal cost.

T lymphocytes maintain chronic inflammatory skin diseases. In healthy skin, two subsets of epidermal CD8⁺ T cells reside, CD49a⁺ tissue- resident memory T cells (T_{RM}) cells provide protection against viral infections and accumulate in vitiligo whereas CCR6⁺ IL-17 and IL-22 producing T_{RM} cells provide protection against fungi and are found in psoriasis-afflicted skin years after resolution. It is unclear why and how these pathogenic T cells are retained in human skin and the translational skin immunology group focus on discovery-based projects to understand a) basic principles of T cell migration, residency and renewal in the skin and b) how resident T cells participate in the dynamic disease manifestation of inflammatory skin diseases.

During 2022, projects, methods and knowledge was transferred from the Eidsmo laboratory at Karolinska Institutet as new students and postdocs were recruited to SIC. By a real team-effort over the last year(s), projects from the Karolinska site are finalized or expanded at SIC. Establishing a new laboratory opens up for new perspectives and directions and a major direction going forward will be to set up in vivo models



to study T cell biology in human skin. For this, Rasmus Agerholm-Nielsen and Trine Schoenfeldt are setting up methods to follow T cell behavior in vivo supported by multiphoton microscopy.

A long-standing collaboration with the Bryceson group at Karolinska Institutet is finally in press, with amazing efforts by Elena Hoffer and Wenning Zheng in both Sweden and Denmark. High resolution single cell transcriptomic and bulk epigenetic analysis of migrating and skin resident T cells, combined with functional experiments using CRISPR/Cas9, showed that migrating blood derived T cells are dependent on the transcription factors RUNX2 and RUNX3 to develop into cytotoxic resident T cells. Molecular signatures of RUNX⁺ cytotoxic T_{RM} cells in tumor material were associated with prolonged survival and our findings may become relevant for patients living with metastatic melanomas (Zitti, Hoffer et al, Immunity In Press). Elena and Wenning and the whole lab have now joined forces to understand local renewal of T cells within the skin environment.

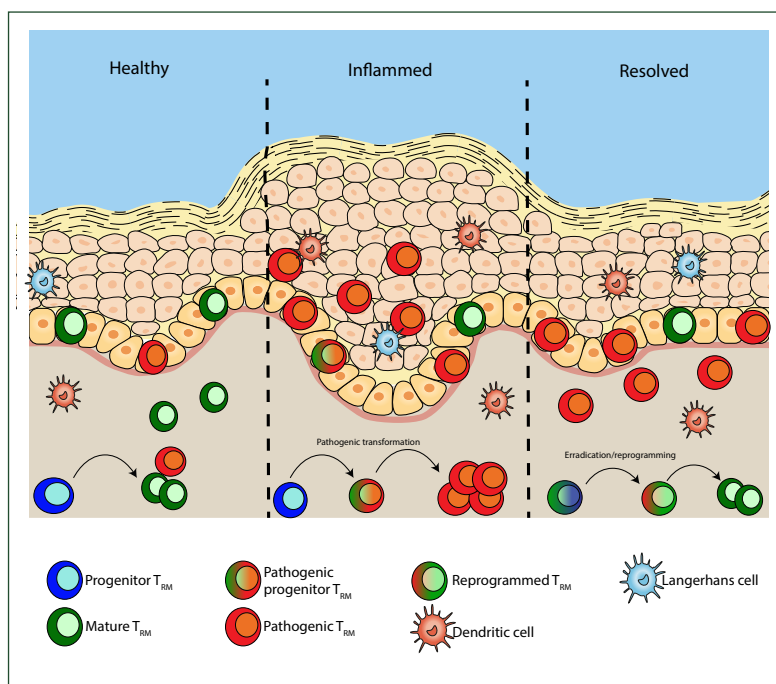
Another long-term project that migrated from Karolinska to SIC focused on how resident T cells initiates disease was finalized in 2022 by Borislav Ignatov, Trine Schoenfeldt and Daniel Sortebeck.

In human allergic contact dermatitis, resident T cells activate surrounding stroma cells to produce the tissue remodelling metalloproteinase 12, which combined with T cell derived cytokines disrupted the epidermal structure and basement membrane (Gallais-Serezal et al, Allergy). Borislav Ignatov and Ekaterina Zhuraleva are now mapping distinct mechanisms of pathology initiated by resident T cells in vitiligo and altogether, these studies are showing us how important it is to have just the right amount and balance of T cells in the skin.

Finally, the group always strive for clinical relevance and the translational potential of our mechanistic studies are currently tested in a global clinical study as a clinical study on early intervention in psoriasis is coming to an end (Iversen et al, JEADV). It is hopeful to follow the development of new drugs available for neglected autoimmune skin diseases such as Hidradenitis suppurativa and vitiligo (Eidsmo, NEJM). Through close collaborations with dermatologists in Copenhagen, combined with

the excellent patients registers in Denmark, our clinical fellows Albert Duvetorp, Daniel Sortebeck and Rune Kjearsgaard Andersen are investigating different biomarkers and disease trajectories of psoriasis, vitiligo, and hidradenitis suppurativa.

The group is now at full capacity and the process of migrating research and recruiting scientists into a new site coincided with our studies of the same processes in T cells. These parallel processes have spurred stimulating discussions on basic principles of migration for T cells and people. As the findings on the new establishment of T_{RM} cells are in press, we look forward to focusing all efforts to understand how cells and people renew and mature in situ during 2023.



Skin resident T cells form localized disease scars in psoriasis.

Professor

/// Liv Eidsmo

Lab manager

/// Maja Soeberg Udsen

Lab technician

/// Marta Madacsi

Clinical Fellows

/// Albert Duvetorp
/ Rune Kjearsgaard Andersen

Postdocs

/// Ekaterina Zhuraleva
/// Wenning Zheng
/// Rasmus Agerholm-Neilsen

PhD students

/ Borislav Ignatov
/ Elena Hoffer
/// Trine Schoenfeldt

MSc, MD and BSc students

/// Daniel Sortebeck
/ Fie Bendix
/ Liva Herlenius
/ Valeria Magnuson
/ Chenming Zhang

Bioskin

Based on an add-on grant from the LEO Foundation, SIC and Herlev and Gentofte Hospital initiated the 'Copenhagen Translational Skin Immunology Biobank and Research Program' (BIOSKIN) in 2021. The program is a prospective biobank and research study collecting clinical data and biological samples from 3,000 patients with the most prevalent chronic inflammatory skin diseases; psoriasis, atopic dermatitis and contact eczema. The program is headed by Clinical Professors Jeanne Duus Johansen and Lone Skov.

The Copenhagen Translational Skin Immunology Biobank and Research Program (BIOSKIN) is a prospective biobank and research study following patients with the most prevalent chronic inflammatory skin diseases; psoriasis, atopic dermatitis and contact eczema. The aim of the program is to intensify translational research in dermatology by collecting high-quality biological samples and clinical data from 3,000 patients over a period of minimum five years. The core elements of the program are a comprehensive biobank, a set of clinical studies and cutting-edge research technologies in skin immunology. The longitudinal open cohort design with repeated sampling will allow participants to enter and leave the study at different time points during monitoring. Together this will enable a thorough characterization of the patient's disease trajectories, response to treatment and risk of comorbidities among others. Ultimately, the results from this research program will improve the quality of life for a large group of patients and lead us closer to a cure for disabling inflammatory skin diseases.

The biobank is anchored at the Department of Dermatology and Allergy, Herlev-Gentofte Hospital. The study was approved by the Regional Ethical Committee and the Danish Data Protection Agency early in 2022 whereafter patient inclusion started. In 2022 the primary focus has been to consolidate and integrate the research program into the clinic. Further, to escalate the recruitment procedure, the staff has been expanded and now includes three medical PhD students, three project nurses and a lab technician among other.

The initiated PhD studies are dedicated to objectives in differentiation between allergic and irritant contact dermatitis and immunological characterization of subtypes of psoriasis and atopic dermatitis, respectively.

Patient inclusion, follow-up and collection of samples are performed by the BIOSKIN staff at the research unit when the patients meet for a scheduled routine clinical visit. Patients that do

Clinical Professors

- / Jeanne Duus Johansen
- / Lone Skov

Head of Research

- /// Marianne Bengtson Løvendorf

PhD Students

- /// Anne Sophie Heinrichsen
- /// Christina Yndal Erichsen
- /// Marie Mila Broby Johansen

Associated PhD Students

- / Charlotte Sigrid Erika Näslund Koch
- / Morten Bahrt Haulrig

Project nurses

- /// Ditte Viborg Petersen
- /// Helene Meyer Martin
- /// Rikke Juul Wittrup

Lab technician

- /// Gitte Stæhr Hemmingsen

Master Student

- / Guðrún Nanna Árnadóttir



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, have been integrated in the daily clinical practice. Employees in BIOSKIN include among others medical PhD students, project nurses and a lab technician.

not follow a clinical course at the Department of Dermatology and Allergy, Herlev and Gentofte Hospital will be recruited from advertising using various public platforms. Biological samples will be collected at every visit and as a minimum patients > 18 years old provide a blood sample and when accessible and relevant, we also collect samples from lesional, non-lesional and healed skin including punch biopsies, tape strip samples and skin swaps. We may also collect feces samples and conduct skin prick and patch tests on a project-based initiative. Preanalytical factors including date and time of sampling, handling, storage, and the exact handling procedure are recorded in the nationwide Bio- and Genome Bank Denmark registry (RBGB) and the Capital Region hospitals' freezer facilities (BIOSEK) are used for long term storage of the samples.

As part of the organization of BIOSKIN a patient board representing patients with psoriasis, atopic dermatitis and contact eczema has been established to ensure integration of the patients' perspective and the needs of future patients into the research program. Furthermore, BIOSKIN has a close collaboration with patient organizations such as the Danish 'Psoriasis Association', 'Atopic Eczema Association' and Astma-Allergy Denmark.

Together, the BIOSKIN program will entail unprecedented biological sampling, clinical assessments, and collection of patient data. By the end of 2022 around 350 patients were enrolled in BIOSKIN. The program will strengthen the integrational approach between basic and clinical science and result in a large biobank of extremely high value not only for SIC researchers, but also for collaborators nationally and internationally.

Education and career development

PHD COURSE

The LEO Foundation Skin Immunology Research Center offers five spots for international PhD students to participate in the center's PhD course on innate immune signaling pathways on 24-27 January 2022.



About the course

The aim of this PhD course was that participants acquire knowledge on innate immune signaling pathways and regulations thereof both in response to microbes (commensals and pathogens) and in inflammation in states of disease in skin and gut. Focus was on the molecular mechanisms that govern the early immune responses and on post translational modifications that occur, how they can be regulated and potential consequences of deregulation. In addition, there were presentations on pharmacological interventions to deregulated responses.

The course included a journal club where students presented pre-selected papers to each other, and meet-the speaker sessions, where

students met with the invited speakers of the course.

The course contained lectures by leading researchers within the fields immune signaling both from SIC, from Danish research institutions and internationally.

Learning objectives

The objectives of the course were:

1. Explain concepts governing activation of innate immune responses
2. Describe signaling pathways and post-translation modifications involved in immune signaling
3. Have examples of how deregulation of innate immune signaling can lead to disease
4. Explain the interplay between the host and microbes
5. Discuss techniques for addressing outstanding questions in the field and address their strengths and weaknesses

Organisers

The course was organised by Assistant Professor Berthe Katrine Fiil and Professor Mads Gyrd-Hansen from the Molecular Immunology and Inflammation Group at SIC.

INTERNATIONAL STUDENTS AT SIC



Daniel Sortebeck – one of six international Masters students at SIC.

Through the years many international students have been hosted at SIC. This year we have had the pleasure of hosting six international master students. Hanna Alena Kulvicki completed her bachelor's degree at Vienna and is now doing a master's degree in Immunology and Inflammation at Copenhagen university and is writing her thesis in the Molecular Immunology and Inflammation group. Daniel Sortebeck is a medicine student from Karolinska university, and he is doing his research project in the Translational Skin Immunology group. Alexandra Seibel completed her bachelor's project at Strasbourg university and completed a 3-month ERASMUS project in T cell Biology and Skin Inflammation group.

When asked about their motivation when applying for a project abroad they all agreed that they saw it as an opportunity to accelerate their academic carrier and personal growth.

"I wanted to test out different universities before deciding where I wanted to do my master's degree and I saw it as an opportunity to grow both as a researcher and an individual"

- Alexandra Seibel

Furthermore, they were intrigued by the beautiful location of the Centre and the core facility associated with the department of immunology and microbiology. The students

have been introduced to new methods like; microscopy, slide scanner, western blotting, qPCR, ELISA, Incucyte machine, CRISPR/ CASE, as well as working with both mice and cell lines. Together with being introduced to new methods, the students have also expressed that the experience has expanded their academic network and made them feel more confident within the academic field.

"My master's project is very relevant for the master's degree I'm doing"

- Hanna Alena Kulvicki

Hanna expressed that the combination of the SIC lunches and ISIM talks initiatives makes it easier to get an understanding of the research which is being performed at the department and who it might be relevant to connect with, thereby making it easier to broaden one's academic network.

"I have definitely built my academic network more here compared to back home, which is why I decided to do my masters here"

- Hanna Alena Kulvicki

The supportive environment at the centre makes it possible for the students to improve their academic skills in a supportive environment with access to top laboratory equipment which they would not have had access to back home.

"You have great facilities and staff who are happy to help you if you have any problems"

- Daniel Sortebeck

After completing a research project at the centre this summer Daniel decided to return for his master's project. Moreover, both Hannah and Alexandra have expressed an interest in continuing their academic carrier at the centre. Showing the appeal of SIC and the Danish cultures appeal to international students. All three expressed an appreciation for the work-life balance displayed at the centre.

SUMMER SCHOOL

Inspiring days at SIC Summer School discussing “Immune Regulation of the Skin”.

When spring arrived in Denmark, so did some of the world’s leading researchers within skin immunology to join the SIC Summer School 2022. The Summer School is an exclusive chance for young and talented researchers to meet and learn from leading experts.

For the second time in history, the LEO Foundation Skin Immunology Research Center, University of Copenhagen, organized an intense three-day learning experience on skin and immunological skin disease research. The Summer School offers 1:1 interaction with and feedback from leading experts on this year’s theme: ‘Immune regulation of the skin’.

During the intense days, a great outline of speakers gave their newest insights on the role of T cells in skin development and inflammation, regulation and danger sensing mechanisms, and the regeneration of wounded skin.

International Speakers

To kick off the SIC Summer School, Professor Robert L. Modlin flew in from UCLA Health to talk about ‘Regulation of danger sensing in the skin’.

“I am so happy to be here. I am happy to be out of California, out of LA, even out of my house after all this time of COVID-19,” Dr. Modlin started out before his inspiring opening talk.

Dr. Modlin’s laboratory has made fundamental insights into T cell subsets, cytokine patterns, antigen presentation, innate immunity, and



antimicrobial mechanisms in the human immune response to infection.

On another international note Shoba Amarnath from Newcastle University talked about Gate Keepers to Immune Tolerance. And William Crisler from HMX – Harvard Medical School talked about T cells Rejection in Vascular Composite Allotransplants.

A huge thank you to all speakers who took the time to participate!

From 2023, The Summer School will be renamed Springtime School.



SUPERVISED PHD, MASTER, AND BACHELOR STUDENTS

Bachelor

Emilia Sæderup Lindeløv, Bachelor thesis, *Cathelicidin regulation in macrophages in the absence and presence of Vitamin D*, supervised by Martin Kongsbak Wismann.

Fie Bendix Thomsen, Bachelor thesis, *The impact of the extracellular environment on the differentiation of skin resident T cells from the blood*. Supervised by Liv Eidsmo.

Daniel Sortebeck, International student, *Characterisation and anatomical niche of CD62L⁺ T cells in human skin*. Supervised by Liv Eidsmo.

Liva Herlenius, Bachelor thesis, *Techniques to study human skin T cells*. Supervised by Liv Eidsmo.

Master student

Louise Aagaard, master student, *Heat-killed Mycobacterium tuberculosis destabilizes the vitamin D receptor in human macrophages*. Supervised by Carsten Geisler and Martin Kongsbak-Wismann.

Julie Weber, master student, *Determining regional and age-related differences in the cellular composition of healthy human skin using Single-cell RNA sequencing*. Supervised by Charlotte Menné Bonefeld.

Miriam Beichler, Erasmus student, *Masters program: Investigation of Z-NA Binding Protein 1 (ZBP-1) and Z NA localisation and the role of ZBP 1 in NF-κB signalling*. Supervised by Mads Gyrd-Hansen.

Rebecca Sturm, Erasmus student, *Master Thesis: Characterisation of Met1 ubiquitin regulating proteins*. Supervised by Mads Gyrd-Hansen.

PhD students

Fatima Abdul Hassan Al-Jaberi, PhD titel, *Novel insights in vitamin D receptor-based immune regulations*. Supervised by Carsten Geisler and Martin Kongsbak-Wismann.

Maria Teresa Martin Monreal, PhD title, *Influence of peptidyl arginine deiminases on immune responses to self-antigens*. Supervised by Niels Ødum.

Cheng Chi, Phd title, *Concomitant Inhibition of FASN and SREBP Provides a Promising Therapy for CTCL*. Supervised by Anders Woetmann.

YOUNG INVESTIGATOR NETWORK



In 2022, the Young Investigator Network (YIN) organized five exciting meetings, bringing together early career researchers and doctors in the dermatological field. Based on feedback from attendees at previous meetings, the YIN is a dynamic group with freedom to explore and discuss the many challenges early-career researchers face – be they professional or personal.

Meetings in the YIN usually consist of a visit to an interesting place or a talk by an invited speaker, followed by socializing in the form of small games, designed to “break the ice”, while sharing a meal. The YIN believes this two-fold structure leads to curiosity, interesting scientific discussions and ultimately cross-collaborative scientific output between members of the network.

The five events held in 2022 were:

In March, we went for a guided tour around the Medical Museion and its COVID-19 exhibition. The tour highlighted some of the many changes our lives took during the pandemic and how biomedical science was integral in keeping the pandemic under control. In addition, the exhibitions told stories of how, not long ago, infections, today regarded as simple, were often lethal. Together, we were reminded of the importance of medical research. This was of course a great motivator for our attendees to press on with their projects.

In May, we went to LEO pharma in Ballerup learning about career opportunities outside of academia, and how maintaining professional contact can help facilitate collaborations and open new career possibilities. We heard talks and interacted with the Vice President of Research and Early Development, Thorsten Thormann and Senior Principal Scientist, Paola Lovato, among others.

In September, we invited Mette Fog Skriver, career guidance counselor at the University of Copenhagen, to talk about career development. The talk was packed with general tips on career pathways and planning, both in the context of academia and industry. It also covered an introduction, especially helpful for our international colleagues, detailing how to structure a CV and motivational letter for the Danish job market.

In October, we had a hands-on workshop with Mette Løgeskov Lund and Søren Thiesen from the communications department at the Faculty of Health and Medical Sciences, at the University of Copenhagen. Here the focus was on improving communication skills to enable efficient and understandable dissemination of research to audiences not familiar with research projects – both the media and friends and family.

In November, rhetorician and actor Nastja Arcel was invited to do a workshop on oral presentation techniques, voice and appearance. Nastja has previous experience with training early-career scientists as she held a position as performance coach in the PhD Cup. For many of our attendees, this workshop provided tangible tips and eased nerves on looming PhD defenses, lectures and seminar talks.

As the YIN enjoys continuous support from both its members and funding institutions, the planning committee are full of work, creating exciting meetings in 2023 were we look forward to bringing together both old and new faces.

THE YOUNG INVESTIGATOR NETWORK

- ‡ Was established in 2019 by early-career researchers from SIC and clinical dermatological departments in the Copenhagen area
- ‡ Aims to establish collaborations between researchers and clinicians in the field of immunology and dermatology
- ‡ Has approximately 100 active members and a turnout of around 35 members per meeting
- ‡ Is always looking for new members (if you are an early-career scientist or doctor working in the cross-field of immunology and dermatology, contact sic@sund.ku.dk)

Planning committee, 2022

Martin Kongsbak-Wismann (Chair)
Berthe Katrine Fiil
Emil Marek Heymans Pallesen
Anne-Sofie Østergaard Gadsbøll
Pernille Lindsø Andersen
Sofia Botvid
Yasemin Topal
Dorra Bouazzi
Farnam Barati Sedah
Jennifer Astrup Sørensen
Stine Kloppenborg

MINI COURSE IN SKIN IMMUNOLOGY FOR SECONDARY SCHOOL STUDENTS

Following the success from last year SIC recreated the mini-course in skin immunology for third-year secondary school students at Gefion Gymnasium.

This year the spotlight was on biotechnology which combines biology and chemistry. During the two-day course, the young students gained insights into skin and immunology through a practical hands-on approach where they worked in the laboratories alongside the researchers at SIC. This authentic approach generates vigorous opportunities for interactions between the students and our researchers. In this way, our researchers are challenged to refine their sci-com abilities and the students get a chance to ask questions, satisfy their curiosity and test their knowledge.

Over the next few years, SIC plans to annually give third-year students from Gefion Gymnasium the unique opportunity of this inspirational mini course.

Feedback from the teacher at Gefion Gymnasium:

“Thank you for two unforgettable days. It has been truly amazing for our students to explore your research environment and getting hands-on experience with some of your difficult research techniques”

Organisers

Anders Woetmann
Charlotte Menné Bonefeld



Malin Jessen - PhD Student

CYLD-SPATA2-LUBAC complex regulates skin inflammation

Regulation of signaling processes in innate and adaptive immune cells is crucial for the immune response to stay in balance. Dysregulation often leads to autoinflammation and immunodeficiencies with tremendous consequences for the health of the individual. Ubiquitination is a posttranslational modification that regulates most cellular processes, including signaling by immune receptors. Ubiquitin chains linked via the lysines at position 48 (K48) of ubiquitin facilitate proteasomal degradation of the modified protein whereas ubiquitin chains assembled via K63 and M1 in ubiquitin play a crucial role in mediating pro-inflammatory signalling by immune receptors.

M1-linked Ub chains are assembled by the linear Ub chain assembly complex (LUBAC) following

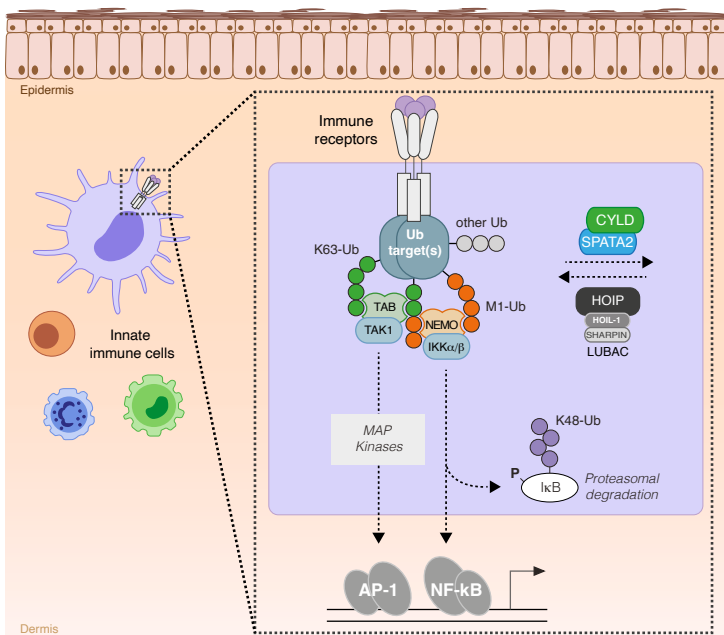
stimulation of cytokine receptors and pattern recognition receptors, resulting in the activation of the transcription factor NF- κ B and MAP kinase cascades.

LUBAC is composed of three subunits: HOIP, HOIL-1 and SHARPIN. To tightly regulate its function, LUBAC forms complexes with the deubiquitinases (DUBs) OTULIN and CYLD. OTULIN directly interacts with the LUBAC subunit HOIP whereas CYLD interacts via the adaptor protein Spermatogenesis-associated 2 (SPATA2). CYLD specifically cleaves both K63- and M1-linked Ub chains and is known to be a negative regulator of NF- κ B signaling. In humans, mono-allelic mutations of CYLD predisposes to development of benign cutaneous tumors (e.g. cylindromas) and somatic CYLD mutations have been linked to human head and neck cancer.

Previous work by the group has shown that SPATA2, by linking CYLD and LUBAC, regulates signaling but the physiological role of the CYLD-SPATA2-LUBAC complex remains poorly understood. My project aims to decipher its role during skin inflammation using different experimental mouse models. This allows us to explore its contribution to disease-like phenotypes such as dermatitis and psoriasis. Our preliminary data indicate that SPATA2 contributes to the onset of chronic proliferative dermatitis (cpdm) in mice deficient for the LUBAC subunit SHARPIN. In contrast, in an psoriasis-like model, SPATA2

appears to attenuate skin inflammation. This highlights that the consequence of disrupting the CYLD-SPATA2-LUBAC complex, and hence the molecular pathways affected, is dependent on the stimulus that triggers skin inflammation. Ultimately, my research may advance our understanding of CYLD and SPATA2 as potential therapeutic targets in inflammatory skin diseases.

The project aims to understand the role of CYLD and SPATA2 in regulating innate immune signaling during skin inflammation.



PHD PRESENTATION

Regulation of LUBAC function and M1-linked ubiquitin

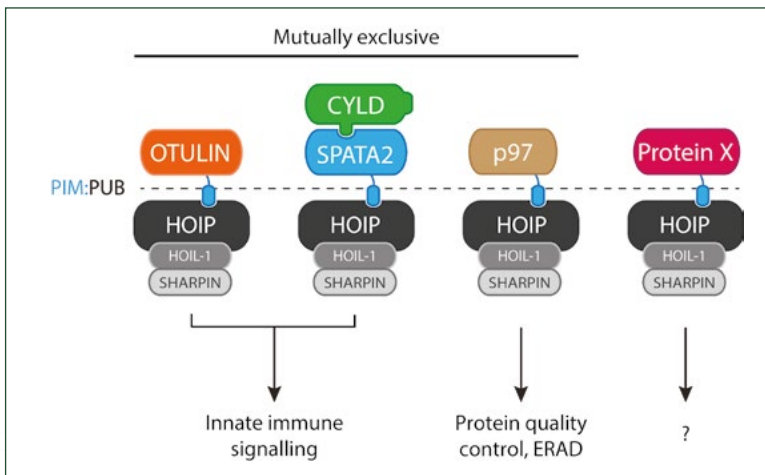
The posttranslational modification of proteins by ubiquitin is fundamental for most cellular processes, including signaling by immune receptors. Proteins may be modified by one or more ubiquitin molecules that can be assembled into polymeric chains via conjugation of the C-terminus of one ubiquitin to one of seven internal lysines (K), or the N-terminal methionine (M1) of another. Ubiquitin chains linked via the lysine at position 48 (K48) of ubiquitin facilitate proteasomal degradation of the modified protein, whereas ubiquitin chains assembled via K63 and M1 play a crucial role in mediating pro-inflammatory signaling by immune receptors.



Frederik Timmermann - PhD Student

infections without causing autoinflammation and autoimmunity.

The overall aim of my PhD project is to explore the molecular mechanisms by which LUBAC is regulated, with the goal to better understand how M1-linked ubiquitin contributes to protective vs. pathological inflammation. Previous work by the group and others revealed that LUBAC forms mutually exclusive complexes with the two deubiquitinating enzymes (DUBs) OTULIN and CYLD-SPATA2, as well as with the highly abundant ATPase p97/VCP. These complexes are formed through a conserved interaction with the PUB domain in HOIP. Employing proteomics-based approaches, I am investigating if LUBAC may have additional binding partners that regulate LUBAC activity directly or link LUBAC to undescribed cellular processes regulated by M1-linked ubiquitin chains. A second part of my project is to explore if LUBAC activity is regulated in a cell- or tissue-specific manner through differential expression of LUBAC and its interactors. To address this, I am quantifying absolute abundances in a range of cell types and tissues, using quantitative proteomics. This part of the project is a collaboration with other groups at SIC and researchers at DTU. In the long term, I hope my research will improve our understanding of the regulatory mechanisms that control LUBAC and M1-linked ubiquitin chains, and thereby the role of M1-linked ubiquitin in inflammatory skin diseases and potentially other immune-mediated diseases.



The project addresses the regulatory mechanisms that control LUBAC complex formation and aims to identify additional binding partners that influence LUBAC activity or recruit it to other cellular processes.

LUBAC (The linear ubiquitin chain assembly complex) is the only known ubiquitin ligase in the cell that generates M1-linked ubiquitin chains and hence is key for immune regulation and inflammation. It is a trimeric complex that consists of the catalytic subunit HOIP and two regulatory subunits, HOIL-1 and SHARPIN. Genetic mutations that alter the function of LUBAC lead to severe pathophysologies, including impaired immune responses, deregulated inflammation, and chronic proliferative dermatitis. This illustrates that LUBAC and M1-linked ubiquitin chains must be carefully regulated to ensure immunity to



Mila Broby Johansen - PhD-student

Subtypes of psoriasis vulgaris

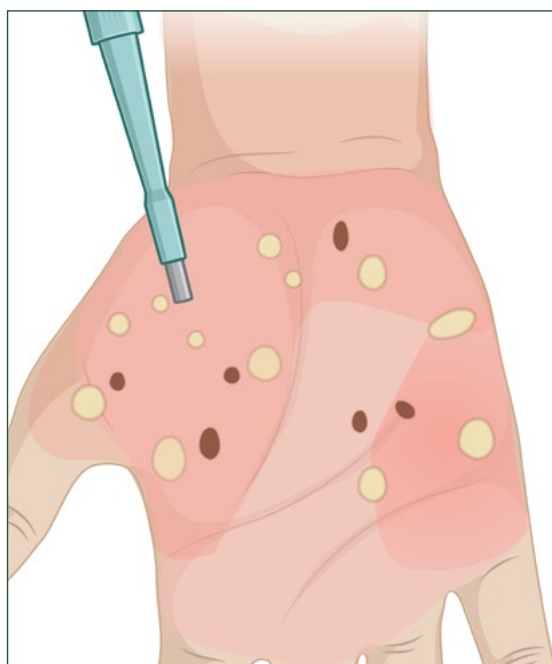
Psoriasis is a multifactorial disease with a combination of genetic, environmental, and immunologic factors as well as comorbidities. The pathogenesis of psoriasis involves a combination of both the innate and adaptive immune systems and is mainly driven by the Th1 and Th17 T cells/IL-23 axis. Different forms of psoriasis have been described in the literature. They have been classified according to morphology, location, inflammation type, or onset of disease. However, no exact consensus has been reached. Additionally, the different forms can be associated with different genetics and lead to activation of different cytokines and chemokines.

In this study, our overall aim is to investigate whether clinical findings, as well as immunological and molecular biological methods, can be used to distinguish between 1) clinical subtypes of psoriasis vulgaris and 2) palmoplantar psoriasis, palmoplantar pustulosis, and hyperkeratotic hand eczema.

Some studies have tried to distinguish subtypes of psoriasis vulgaris according to morphology, location and paraclinical variables, but there is still no consensus. We know a lot about the immunological changes of psoriasis, but plaques psoriasis can look different, have different disease courses, and respond differently to treatments. We, therefore, wish to look at unique molecular signatures in different subtypes of psoriasis vulgaris. Furthermore, are there different molecular signatures at different localizations and does it change over time?

Palmoplantar psoriasis (PP) is a subtype of psoriasis that is difficult to diagnose since its classification is based on location, rather than on morphology. The most common differential diagnosis of palmoplantar psoriasis is palmoplantar pustulosis (PPP) and hyperkeratotic hand eczema (HHE). Clinical it can be very difficult and sometimes impossible to differentiate between the three diseases. Few studies have attempted to distinguish the three diseases histopathologically, immunologically or by dermoscopy. We, therefore, wish to distinguish PP, PPP and HHE based on the clinically observable skin disease manifestation, the skin disease history and treatment response. Furthermore, are there different molecular signatures in the three diseases and do they change over time?

The data we are using is from thorough clinical examination, treatment response and follow-up as well as molecular-biological and immunological characterization from skin biopsies and tape strips. Through the studies from the BIOSKIN program we hope to improve diagnostic accuracy, our understanding of the mechanisms of the diseases and subtypes, and potentially identify new biomarkers and therapeutic targets.



Punch biopsy is taking from a hand with palmoplantar pustulosis (PPP). Created with BioRender.com

PHD PRESENTATION

Spatial composition and eradication of T cells in the skin

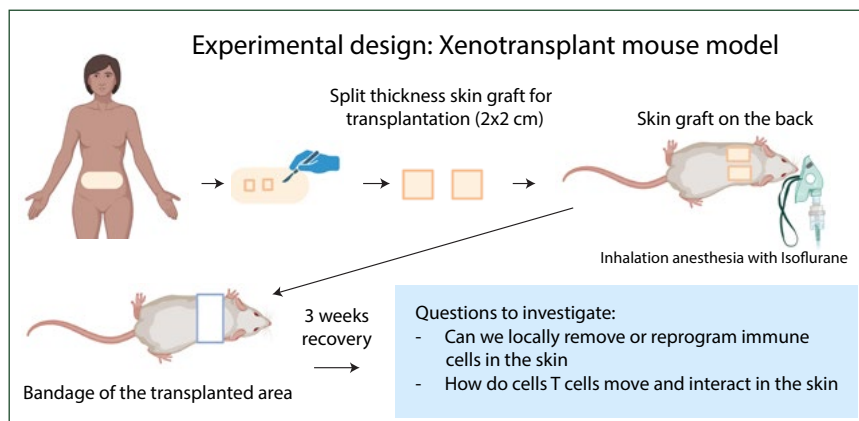
This research project aims to find methods to test if focal eradication of T cells in human skin could serve as a novel therapeutic strategy for relapsing inflammatory skin diseases. Despite complete resolution following efficient therapy, chronic inflammatory skin diseases, such as psoriasis, preferentially resurface/relapse in or return to in resolved areas of the skin during flares of disease activity. Pathogenic tissue resident memory T (T_{RM}) cells are retained in resolved lesions and when reactivated, these cells cause disease relevant tissue pathology, thereby creating immunological scars of disease in the skin. We postulate, that therapies that allow elimination or long-term suppression of disease-driving T_{RM} cells will provide cure or superior remission compared to current treatments. Taken that the composition, distribution, and interactions of different subsets of T cells is not fully mapped within the human skin, the first goal of the thesis work is to map the spatial composition and interactions of T cells in healthy and resolved human skin. Confocal microscopy, AxioScan and computational analysis, including development of a machine learning tool enables consistent, faster, and reliable 3D maps of the spatial distribution of T cells within the skin in comparison with manual assessments.

The second part of the PhD project aims to locally eradicate T cells in healthy human skin. Drug-loaded microneedle plasters will be applied to a humanized xenotransplant model established by co-supervisor Melican



Trine Schønfeldt - PhD Student

at Karolinska Institutet. This allows for in vivo studies of renewal and modulation of local T cell populations and drug-loaded microneedle plasters in collaboration with a group at Karolinska Institutet who has the expertise and knowledge required for the development, production and stability tests. Thus, this project is performed in close collaboration with partners at Karolinska Institutet which allows for technical transfer of skills and tools to SIC. In the xenotransplant model we transplant human skin to immunodeficient mice. We use excessive human skin from plastic surgical procedures delivered by our collaborating plastic surgeons in Copenhagen. Three weeks after transplantation the skin is ready for further experiments, such as T cell eradication experiments with application of our drug-loaded microneedle plasters. Microneedle plasters allow penetration of the epidermis and drug delivery around the basement membrane where pathogenic T_{RM} cells are located. The long-term goal is to provide scientific data that may serve as a basis to create the treatments of tomorrow for chronic inflammatory skin diseases.



We get excess skin from our plastic surgical collaborators and use it in our xenotransplant model. In this model we transplant human skin onto immunodeficient mice which allows in vivo experiments on human skin (illustration created with BioRender.com).



Helen Vaher - Marie-Curie Fellow

The role of microRNAs in the regulation of the generation and maintenance of skin resident memory T cells

Contact allergy (CA) to at least one allergen is common in the European population with a prevalence of 27% of which CA to nickel is the most frequent with a prevalence of 8% to 19%. Moreover, CA can develop into allergic contact dermatitis (ACD), which is an inflammatory skin condition characterized as a delayed-type hypersensitivity reaction manifesting as skin rash and localizing to the site of skin contact. Based on its prevalence, ACD is considered a general health problem resulting in decreased quality of life for many people. Recent studies show

that allergen-specific epidermal skin resident memory T (T_{RM}) cells, defined by being $CD8^+$ $CD69^+$ $CD103^+$ $\alpha\beta$ T cells, are important in ACD. Previous results show a huge change in the epidermal T cell composition with allergen-induced T_{RM} cells comprising approximately 60% of the epidermal T cells and they recruit neutrophils into the epidermis that are driving the flares seen in the skin.

MicroRNAs are short non-coding RNA molecules that regulate gene expression at the post-transcriptional level and affect numerous biological processes. It is known that particular miRNAs are capable of inhibiting inflammatory responses in the skin e.g. in keratinocytes. Numerous other studies have shown miRNA-mediated regulation to be important in adaptive immune responses, however, the role of miRNA functions in the development, regulation, and maintenance of memory $CD8^+$ T_{RM} cells in the skin has been overlooked. The aim of the project is therefore to identify molecular and epigenetic pathways that microRNAs might affect to either develop or contribute to the persistence of ACD. As the skin T_{RM} cells also contribute to the development of psoriasis and vitiligo, the studies could also lead to viable and novel treatment strategies for other skin diseases.



POSTDOC FELLOWSHIP PRESENTATION

Targeting the tumor microenvironment in mycosis fungoides

Mycosis fungoides (MF) is the most common subtype of primary cutaneous T cell lymphoma (CTCL). It is usually an indolent disease with limited patches and plaques; however, approximately one third of the patients experience progression to advanced disease stage encompassing ulcerating tumors and systemic dissemination. What drives the transformation of an indolent disease to a highly aggressive cancer with a dire prognosis is poorly understood. To date only allogeneic bone marrow transplant represents a potential cure in CTCL. Thus, there is a desperate need for new treatment strategies.

To prevent disease progression, we need to dissect the underlying mechanisms driving the transition. Recent years focus on the tumor microenvironment (TME) in MF has brought new insights into the molecular landscape of MF, and novel therapeutic strategies have emerged, including immunotherapy demonstrating promising results in MF.

We have previously reported an abundant presence of B cells in the TME of MF compared to benign inflammatory skin disorders. Although we do not know the significance of B cells in MF, they have been linked to both anti- and



Pia Rude Nielsen - BRIDGE fellow

pro-tumorigenic roles in other types of cancer, and appear to have an emerging role in cancer immunity.

This study aims to elucidate the potential pathological role of B cells in MF disease progression. To obtain this knowledge we will combine spatial transcriptomics using NanoString's GeoMx® Digital Spatial Profiler and single cell RNA sequencing on skin biopsies from MF patients. This approach gives us the opportunity to discover unprecedented information of the tumor microenvironment in MF, paving the way for the detection of new treatment targets. Moreover, the insight obtained from deep spatial profiling can further add in recognizing molecular drivers of disease, novel signaling pathways and various cell type function in the microenvironment. In addition, we explore the therapeutic role of B cell directed therapy with an anti-CD20 antibody (Rituximab) in patients with advanced-stage MF.

The project will establish a putative role of B cells in the pathogenesis of MF and clarify if an alternative treatment approach with anti-CD20 can disrupt the potential pro-tumorigenic signals delivered by B cells and thereby reverse disease progression and ultimately postpone death.





Rune Kjærsgaard Andersen - BRIDGE fellow

Constructing an algorithm to help predict disease progression of hidradenitis suppurativa

An estimated 60,000 Danes suffer from an underdiagnosed skin disease called hidradenitis suppurativa. The burden of disease varies and when active disease is allowed to progress, symptoms can become very severe and large areas of scar tissue formation can develop in the inguinal area and other sites where skin meets skin. To avoid disease progression, it is important to treat the patients with the proper medication at an early stage. This project aims to develop an algorithm that can accurately assess the individual's risk of disease progression. Such an algorithm may enable doctors to optimize treatment at an individual level, and may add to the growing efforts to implement personalized medicine within the field of Dermatology.

The project objective is pursued by three separate approaches/aims within the fields of epidemiology, immunology and genetics.

In the first part, parameters linked to progression status will be investigated for the retrieved clinical and demographic information collected at the first clinical visit from 350 patients currently included in dermatological hidradenitis suppurativa database at Zealand University Hospital, Roskilde.

In the second part, serum samples from >100 participants who participated in The Danish General Suburban Population Study and screened positive for hidradenitis suppurativa more than a decade ago will be analyzed by LUMINEX or MESOSCALE assays for the presence of systemic inflammatory biomarkers. Any signs of systemic inflammation will be correlated with levels of progression as determined during follow-up of each participant.

The third part will utilise genetic samples from a large cohort of nearly 2,000 Danish patients with hidradenitis suppurativa that has been collected since 2014. These samples will be analyzed at the facility of our external partner DeCODE genetics in Iceland, and combined with summary statistics from other genetic biobanks (e.g. UK biobank, FinnGen) a polygenetic risk score of the disease will be calculated.

The final algorithm, based on results from each of the three parts, will subsequently undergo *in-silico validation* within the Danish Blood Donor Study that have collected both epidemiological, immunological and genetic information on representative cohort of participants.

If the algorithm proves effective, it can then be implemented as a form of personalized medicine within dermatological clinics.



Outreach and communication

SIC has accentuated its public voice in skin research through various initiatives and events, including the nature and science festival BLOOM, SIC Talks, Tour de Health and the 35th Nordic Congress of Dermatology and Venerology in Copenhagen.

The visibility of SIC has been promoted the past year, according to the planned communication strategy, in which research dissemination is one of the four pillars that continue to set the scene for SIC's outreach activities. The remaining three pillars are: establishing digital platforms, training ambassadors and stakeholder collaborations.

If we traumatize our skin, it has the marvellous ability to heal itself. How is this even possible? And can we translate the ability of certain animals to regenerate whole limbs? Represented by Anders Woetmann, SIC was part of answering and debating these fascinating questions at the popular nature and science festival BLOOM in Denmark. This gave the public a chance to experience a live cross-field discussion encompassing the cutting-edge knowledge within skin immunology, biology, and stem cell research.

The initiative 'SIC Talks' was successfully launched as we welcomed the first seminar by physician-geneticist Hirotsuga Oda from the University of Cologne, giving us the newest insights into genetic and immunological mechanisms of human autoinflammatory diseases. We were also fortunate to host Dr. Pedro Mouro Alves, who is group leader and chair holder (ImmunoHub) at the i3S at University of Porto, Portugal and discovered more about the function of the Aryl Hydrocarbon Receptor in shaping the host immune response to infection.

Charlotte Menné Bonfeld was invited to join a podcast called "SKIN" where she had a lively discussion about how we protect and maintain a healthy immune response in the skin - breaking down the functions of the skin barrier for the listeners.

In connection with Tour de France coming to Denmark, Healthcare DENMARK was invited to host their event 'Tour de Health' in the Mærsk Tower where Liv Eidsmo presented SIC's effort to tackle the challenge of chronic inflammatory skin diseases. The panel discussed asked the question "How do we ensure prevention of chronic diseases in the future with limited economic resources and healthcare professionals?", leading to an intriguing discussion between the international healthcare stakeholders.

Last year's hands-on training in SoMe tailored for SIC's researchers and clinical members of Young Investigators Network continued to bear fruit into 2022 as the ambassador researchers have carried on advancing their sci-com abilities when disseminating research on digital platforms, ultimately creating a higher awareness of the current scientific activities at SIC.

In 2023, the aim will be to advance and expand SIC's visibility, and voice, on digital platforms reaching out to the public, and potential new scientific talent, via targeted communication strategies on SoMe. Moreover, SIC will continue the dialogue with different stakeholders as well as keeping a solid focus on the recruitment of talented researchers and students.



NETWORKING EVENT

From Clinical Observation to New Mechanistic Insights

In May, the dermatology society across the Nordic countries gathered at SIC to enjoy a networking event as part of the 35th Nordic Congress of Dermatology and Venereology in Copenhagen.

Liv Eidsmo introduced Director Ken Arnold from the Medical Museion, UCPH, for his inspiration keynote talk *Curiosity, communication and collaboration within and beyond medical research*.

At the top of the Tower the event brought together both established and early-career scientists in translational dermatology to discuss topics that are vital in promoting high-quality scientific output and productive interdisciplinary collaborations.

Three main questions were discussed in small groups:

- ‡ How do we pave the roads from clinical observations to impactful science?
- ‡ How do we build successful and sustainable career paths for researching dermatologists?
- ‡ How do we form dynamic bonds between dermatologists and preclinical research groups?

Three PhD students – Thomas Emmanuel – Jennifer Astrup – Pernille Lindsø Andersen – summarized the interesting discussions.

Time

Time, and especially time for immersion, is a scarce resource. Therefore, shared positions between clinical work and research should be supported more. However, shared positions carry the risk of having too many tasks at once, decreasing efficiency and creativity. Shared positions could be organized in a semester-based model, as a potentially more efficient and satisfying alternative to dividing the weekdays into the various functions.

RESEARCH

Teamwork

Teamwork should be supported to take advantage of the researcher's individual talents, interests, and competences. Research teams using complementary talents to work on funding, data analysis, writing, project management, and dissemination strengthen individual competences and interests for the benefit of the unit. Teamwork might contribute to a sense of community in contrast to individual competition as experienced by the individual researchers. Teams are furthermore ideal to support the semester-based model for shared positions.

How do we form dynamic bonds between dermatologists and preclinical research groups?

1. Dermatologists and preclinical research groups need to have a basic understanding in plain language of what the other group is doing. The groups must know of each other's existence and how they can synergize.
2. In addition to funding excellent facilities, hospital leadership needs to also prioritize research between dermatologists and clinician groups, with an emphasis on research with potential for momentum. Research also needs to be funded for longer periods at a time.
3. Clinicians very often want to do research but are often inhibited by a lack of time, money, and a place to do so. Clinicians want more help, preferably from a dedicated department, regarding how to acquire more time, money, or a place where dynamic bonds between preclinical research groups can be created.

Thank you to all participants, the Nordic Congress of Dermatology & Venereology and our Organizing Committee members Beatrice Dyring-Andersen and Claus Johansen for making this an inspirational, informative and memorable evening!

Skin lymphoma can lead to severe and even deadly infections. New research at SIC paves the way for prevention.

Skin lymphoma is a rare type of lymphoma. Around 50 Danes are diagnosed with the disease every year. In lymphoma patients, cancer cells are found in different parts of the body and skin, typically in the lymph nodes of the throat, armpit, and groin.

Some patients suffering from severe lymphoma of the skin develop severe and life-threatening infections accompanied by pain and itching.

These infections are a result of skin breakdown which allows bacteria to penetrate the skin barrier. Bacteria then leak into the blood, leading to blood poisoning and other severe conditions.

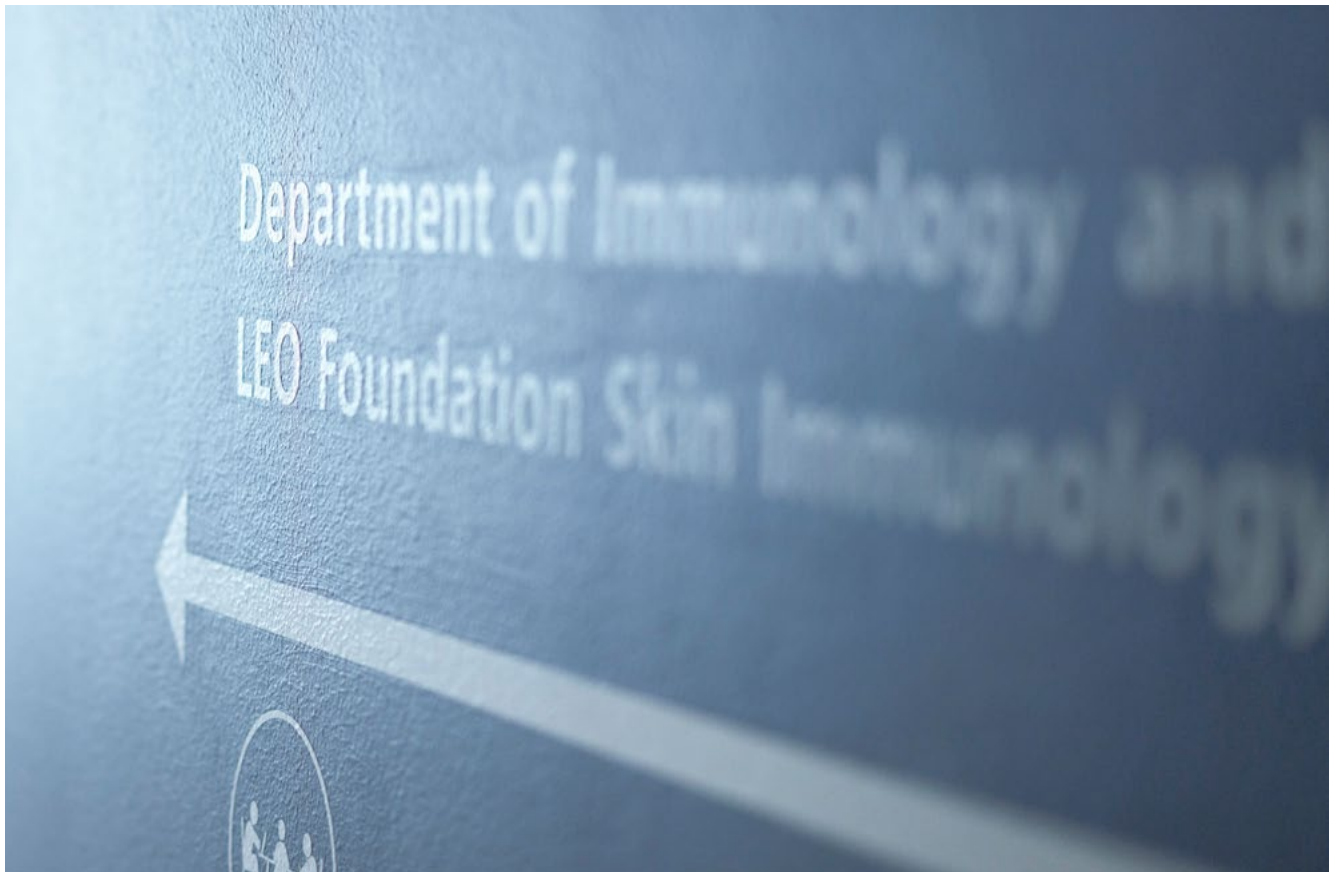
Now researchers from SIC have shown that lymphoma cells emit specific substances that cause the skin to break down and a drug that can prevent the breakdown.

"This discovery is a crucial step in cancer research. In the long term, we will be able to arrest the spread of skin cancer and prevent the life-threatening infections caused by the disease. This will lead to improved diagnoses and quality of life for patients," says Professor Niels Ødum, who has headed the project at the LEO Foundation Skin Immunology Research Center.

The researchers have come a long way towards implementing their results in treatment. The drug able to stop the breakdown of the skin is called JAK inhibitors – and they have already been approved and introduced in the market, though for treating other skin conditions and some types of arthritis.

"This means that we do not have to start over when it comes to testing the drug. We expect to be able to offer the drug to patients in a test environment to see whether it works as expected," says Niels Ødum.

In the study, the UCPH researchers headed by PhD Student Maria Gluud have cooperated closely with Professor Lars Iversen and his team



at the Department of Dermatology at Aarhus University Hospital and Staff Specialist Maria Rørbæk Kamstrup from the Department of Dermatology at Bispebjerg Hospital.

Hopefully to benefit patients soon

They were able to outline the behaviour of the cancer cells and learned how to prevent them from affecting the skin.

“It is a ground-breaking result. It is the first time ever we have seen a method for stopping the breakdown of the skin barrier, which hopefully can help ease the symptoms of the disease,” says Niels Ødum.

“Basically, we have identified the substances produced by the cancer cells and the substances produced by the surrounding cell environment. We have used this to explain why the skin suddenly changes and stops producing the protective layer it is usually covered by,” Niels Ødum explains and continues:

“This has enabled us to conclude that the serious infections found in these patients are

most likely a result of the breakdown of the skin barrier.”

“This leaves us with an important part of the explanation for the breakdown of the skin. And we know that broken skin leads to all kinds of ailments. We have also identified potential paths to preventing this breakdown.”

The researchers hope to be able to launch an experiment soon to test the new discovery on patients, and hopefully their work will soon come to benefit the patients.

The study was funded by the LEO Foundation, the Novo Nordisk Foundation, the Danish Cancer Society (Knæk Cancer) and the Independent Research Fund Denmark.

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 20.9 million, and the turnover from the add-on grants totalled DKK 14.1 million in 2022. Also, SIC obtained a total of DKK 12 million in new funding from seven external research grants.

External research grants awarded in 2022

Funder	Recipient	Title	Amount in DKK
The Danish Cancer Society	Niels Ødum	Stafylokokker forværrer kræften hos patienter med T celle lymfom i huden	2,985,000
BRIDGE, UCPH and Novo Nordisk Foundation	Liv Eidsmo	BRIDGE Fellowship	1,500,000
BRIDGE, UCPH and Novo Nordisk Foundation	Niels Ødum	BRIDGE fellowship	1,500,000
Marie Skłodowska-Curie Actions The European Commission	Helen Vaher	Marie-Curie fellowship	1,719,000
Novo Nordisk Foundation	Jonathan Coquet	Start Up Application	3,000,000
EMBO	Veronika Mraz	Scientific Exchange Grant	46,936
Ellab-Fonden	Lone Skov	Tidlig opsporing af leversygdom hos patienter med psoriasis	1,083,596
Almirall Fund	Lone Skov	Patient with atopic dermatitis' needs for self-management support	200,000

Scientific output

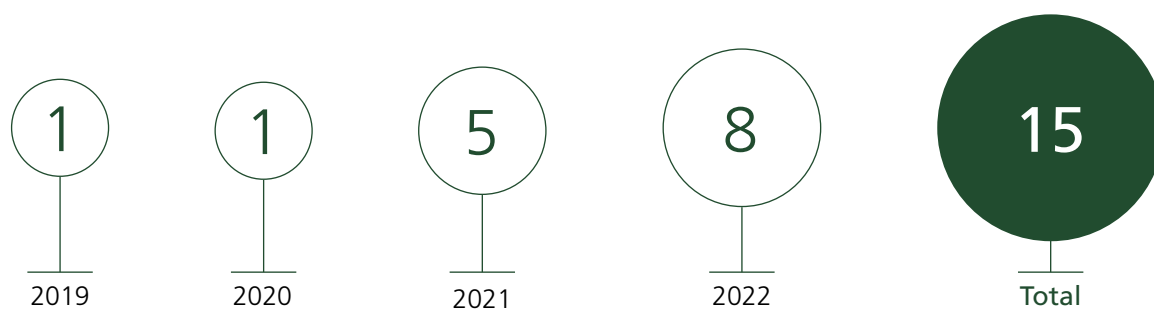
SIC Bioskin researchers authored 27 publications in peer-reviewed journals in 2022. Bibliometric data of senior scientists and a selection of publications of the year are listed here. Sources: Scopus, Web of Science

H-index of senior scientists

Researcher	Number of publications (total)	Number of citations (total)	H-Index
Anders Woetmann	132	5,327	42
Carsten Geisler	205	7,200	47
Charlotte M. Bonefeld	125	3,624	33
Jonathan Coquet	39	2,795	22
Liv Eidsmo	56	3,865	25
Mads Gyrd-Hansen	45	4,194	28
Niels Ødum	320	11,248	58

High-impact publications 2019-2022

Number of publications in high-impact journals (impact factor >10).



Publications

Publications are listed in alphabetical order by article name. Journal and impact factor are in bold.

Assessment of Spatial and Temporal Variation in the Skin Transcriptome of Atopic Dermatitis by Use of 1.5 mm Mini Punch Biopsies.

Hu T, Todberg T, Ewald DA, Hoof I, Correa da Rosa J, Skov L, Litman T.

J Invest Dermatol. 2022 Dec 7;S0022-202X(22)02657-4. **7.60**

Concomitant Inhibition of FASN and SREBP Provides a Promising Therapy for CTCL.

Chi C, Harth L, Galera MR, Torrealba MP, Vadivel CK, Geisler C, Bonefeld CM, Nielsen PR, Bzorek M, Becker JC, Gjerdrum LMR, Ødum N, Woetmann A.

Cancers (Basel). 2022 Sep 16;14(18):4491. **6.58**

FcγRIIIa receptor interacts with androgen receptor and PIP5K1α to promote growth and metastasis of prostate cancer.

Larsson PF, Karlsson R, Sarwar M, Miftakhova R, Wang T, Syed Khaja AS, Semenas J, Chen S, Hedblom A, Ali A, Ekström-Holka K, Simoulis A, Kumar A, Wingren AG, Robinson B, Nyunt Wai S, Mongan NP, Heery DM, Öhlund D, Grundström T, Ødum N, Persson JL.

Mol Oncol. 2022 Jul;16(13):2496-2517. **7.40**

Human ZBP1 induces cell death-independent inflammatory signaling via RIPK3 and RIPK1.

Peng R, Wang CK, Wang-Kan X, Idorn M, Kjaer M, Zhou FY, Fiil BK, Timmermann F, Orozco SL, McCarthy J, Leung CS, Lu X, Bagola K, Rehwinkel J, Oberst A, Maelfait J, Paludan SR, Gyrd-Hansen M.

EMBO Rep. 2022 Dec 6;23(12):e55839. **9.10**

Immune cell composition in unipolar depression: a comprehensive systematic review and meta-analysis.

Sørensen NV, Frandsen BH, Orlovskaa-Waast S, Buus TB, Ødum N, Christensen RH, Benros ME.

Mol Psychiatry. 2023 Jan;28(1):391-401. **13.4**

Induced Human Regulatory T Cells Express the Glucagon-like Peptide-1 Receptor.

Rode AKO, Buus TB, Mraz V, Al-Jaberi FAH, Lopez DV, Ford SL, Hennen S, Eliassen IP, Klewe IV, Gharehdaghi L, Dragan A, Rosenkilde MM, Woetmann A, Skov L, Ødum N, Bonefeld CM, Kongsbak-Wismann M, Geisler C.

Cells. 2022 Aug 19;11(16):2587. **7.67**

Intestinal helminth infection transforms the CD4⁺ T cell composition of the skin.

Classon CH, Li M, Clavero AL, Ma J, Feng X, Tibbitt CA, Stark JM, Cardoso R, Ringqvist E, Boon L, Villablanca EJ, Rothfuchs AG, Eidsmo L, Coquet JM, Nylén S.

Mucosal Immunol. 2022 Feb;15(2):257-267. **9.02**

Knockdown of Circular RNAs Using LNA-Modified Antisense Oligonucleotides.

Løvendorf MB, Holm A, Petri A, Thruue CA, Uchida S, Venø MT, Kauppinen S.

Nucleic Acid Ther. 2022 Nov 23. **4.24**

Knockdown of the long noncoding RNA PURPL induces apoptosis and sensitizes liver cancer cells to doxorubicin

Berhane T, Holm A, Karstensen KT, Petri A, Iliava MS, Krarup H, Vyberg M, Løvendorf MB, Kauppinen S.

Sci Rep. 2022 Nov 14;12(1):19502. **5.00**

Malignant T cells induce skin barrier defects through cytokine-mediated JAK/STAT signaling in cutaneous T cell lymphoma.

Gluud M, Pallesen EMH, Buus TB, Gjerdrum LMR, Lindahl LM, Kamstrup MR, Bzorek M, Danielsen M, Bech R, Monteiro MN, Blümel E, Willerslev-Olsen A, Lykkebo-Valløe A, Vadivel CK, Krejsgaard T, Bonefeld CM, Geisler C, Becker JC, Koralov SB, Iversen L, Litman T, Woetmann A, Ødum N.

Blood. 2023 Jan 12;141(2):180-193. **25.7**

New Hope for Patients with Vitiligo.

Eidsmo L.

N Engl J Med. 2022 Oct 20;387(16):1515-1516. **176**

Novel insights into contact dermatitis.

Johansen, J. D., Bonefeld, C. M., Schwensen, J. F. B., Thyssen, J. P., & Uter, W. (2022).

J Allergy Clin Immunol, 149(4), 1162-1171. **14.3**

Omalizumab serum levels predict treatment outcomes in patients with chronic spontaneous urticaria: A three-month prospective study.

Ghazanfar MN, Bartko EA, Arildsen NS, Poulsen LK, Jensen BM, Enevold C, Holm JG, Woetmann A, Ødum N, Thomsen SF.

Clin Exp Allergy. 2022 May;52(5):715-718. **5.40**

Orally active bivalent VHH construct prevents proliferation of F4⁺ enterotoxigenic Escherichia coli in weaned piglets.

Fiil BK, Thrane SW, Pichler M, Kittilä T, Ledsgaard L, Ahmadi S, Hermansen GMM, Jelsbak L, Lauridsen C, Brix S, Laustsen AH.

iScience. 2022 Mar 1;25(4):104003. **6.11**

Peptidylarginine Deiminase 2 Gene Polymorphisms in Subjects with Periodontitis Predispose to Rheumatoid Arthritis.

Massarenti L, Enevold C, Damgaard D, Hansen PR, Frisch M, Ødum N, Jacobsen S, Nielsen CH.

Int J Mol Sci. 2022 Aug 23;23(17):9536. **6.21**

Preclinical Efficacy of a Capsid Virus-like Particle-Based Vaccine Targeting IL-1 β for Treatment of Allergic Contact Dermatitis.

Goksøyr L, Funch AB, Okholm AK, Theander TG, de Jongh WA, Bonefeld CM, Sander AF.

Vaccines (Basel). 2022 May 23;10(5):828. **4.96**

Psilocybin modulation of time-varying functional connectivity is associated with plasma psilocin and subjective effects.

Olsen AS, Lykkebo-Valløe A, Ozenne B, Madsen MK, Stenbæk DS, Armand S, Mørup M, Ganz M, Knudsen GM, Fisher PM.

Neuroimage. 2022 Dec 1;264:119716. **7.40**

Reduced vitamin D-induced cathelicidin production and killing of Mycobacterium tuberculosis in macrophages from a patient with a non-functional vitamin D receptor: A case report.

Al-Jaberi FAH, Crone CG, Lindenstrøm T, Arildsen NS, Lindeløv ES, Aagaard L, Gravesen E, Mortensen R, Andersen AB, Olgaard K, Hjaltelin JX, Brunak S, Bonefeld CM, Kongsbak-Wismann M, Geisler C.

Front Immunol. 2022 Nov 3;13:1038960. **8.79**

Role of IL-22 in homeostasis and diseases of the skin.

Lopez DV, Kongsbak-Wismann M.

APMIS. 2022 Jun;130(6):314-322. **3.43**

T cells in resolved allergic contact dermatitis steer tissue inflammation and MMP-12-driven tissue modulation

Gallais Séréal I, Tajpara P, Schonfeldt T, Ignatov B, Sortebeck D, Hoffer E, Zhang T, Rooijackers E, Ehrström M, Nylén S, Matura M, Melican K, Eidsmo L.

Allergy. 2022 Dec;77(12):3680-3683. **14.7**

The role of the different CD3 γ domains in TCR expression and signaling.

Garcillán B, Megino RF, Herrero-Alonso M, Guardo AC, Perez-Flores V, Juraske C, Idstein V, Martin-Fernandez JM, Geisler C, Schamel WWA, Marin AV, Regueiro JR.

Front Immunol. 2022 Sep 2;13:978658. **8.79**

The Social and Psychological Impact of Acne Treatment: A Cross-Sectional Study of Blood Donors.

Andersen RK, Bouazzi D, Erikstrup C, Nielsen KR, Burgdorf KS, Bruun MT, Hjalgrim H, Mikkelsen S, Ullum H, Pedersen OB, Ernst Jemec GB.

J Cutan Med Surg. 2022 Sep-Oct;26(5):485-493. **2.85**

Selected publications from BIOSKIN 2022

BIOMAP consortium. Biomarkers of disease progression in people with psoriasis: a scoping review.

Ramessur R, Corbett M, Marshall D, Acencio ML, Barbosa IA, Dand N, Di Meglio P, Haddad S, Jensen AHM, Koopmann W, Mahil SK, Ostaszewski M, Rahmatulla S, Rastrick J, Saklatvala J, Weidinger S, Wright K, Eyerich K, Ndlovu M, Barker JN, Skov L, Conrad C, Smith CH; **Br J Dermatol.** 2022 Oct;187(4):481-493.

11.1

BIOMAP consortium. Biomarkers of systemic treatment response in people with psoriasis: a scoping review.

Corbett M, Ramessur R, Marshall D, Acencio ML, Ostaszewski M, Barbosa IA, Dand N, Di Meglio P, Haddad S, Jensen AHM, Koopmann W, Mahil SK, Rahmatulla S, Rastrick J, Saklatvala J, Weidinger S, Wright K, Eyerich K, Barker JN, Ndlovu M, Conrad C, Skov L, Smith CH.

Br J Dermatol. 2022 Oct;187(4):494-506. **11.1**

Patients with psoriasis have a dysbiotic taxonomic and functional gut microbiota.

Todberg T, Egeberg A, Zachariae C, Sørensen N, Pedersen O, Skov L.

Br J Dermatol. 2022 Jul;187(1):89-98. **11.1**

Prevalence and characterization of treatment-refractory psoriasis and super-responders to biologic treatment: a nationwide study.

Loft N, Egeberg A, Rasmussen MK, Bryld LE, Nissen CV, Dam TN, Ajeiyi KK, Iversen L, Skov L.

J Eur Acad Dermatol Venereol. 2022 Aug;36(8):1284-1291. **9.23**

Topical eye medications causing allergic contact dermatitis.

Ahlström MG, Skov L, Heegaard S, Zachariae C, Garvey LH, Johansen JD.

Contact Dermatitis. 2022 Nov 16. **6.42**

Full staff list

Professors

/ Anders Woetmann
/ Carsten Geisler
/ Charlotte Menné Bonefeld
/// Liv Eidsmo
/// Mads Gyrd-Hansen
/ Niels Ødum

Clinical professors

/ Jeanne Duss Johansen
/ Lone Skov

Associate professors

/ Beatrice Dyring-Andersen
/ Daniel Hargbøl Madsen
// Jonathan Coquet
/// Marianne Bengtson
Løvendorf
/ Martin Kongsbak-Wismann
/// Thorbjørn Frej Krejsgaard

Assistant professors and postdocs

/// Albert Duvetorp
/// Anne-Sofie Østergaard
Gadsbøll
/// Berthe Katrine Fiil
/// Biao Ma
/ Chris Kedong Wang
/// Ekaterina Zhuravleva
// Emil Marek Heymans
Pallesen
/ Helen Vaher
/ John Rizk
/ Katrine Baumann
/ Mandy Menzel
/ Max Benjamin Sauerland
/// Mia Hamilton Jee
/ Morten Orebo Holmström
/// Nicolai Skovbjerg Arildsen
/ Pia Rude Nielsen
/ Rune Kjærsgaard Andersen
/// Rasmus Agerholm
/ Terkild Brink Buus
/// Wenning Zheng

Phd students

/ Anders Boutrup Funch
/// Anne Sophie Heinrichsen
/ Borislav Ignatov
/ Charlotte Sigrid Erika
Näslund Koch
/// Christina Yndal Erichsen
/ Chella Krishna Vadivel
/ Elena Hoffer
/ Eileen Donohue Wedge
/// Frederik Timmermann
// Kelvin Young
/// Lisa Harth
// Malin Jessen
/// Marie Mila Broby Johansen
// Maria Gluud Grøndahl
/// Marina Ramírez Galera
/// Martin Rich Javadi Namini
/ Morten Bahrt Haulrig
/// Shayne Lavondua Ford
/// Veronika Mraz
/// Wenxin Lyu

Research assistants

// Anders Lykkebo-Valløe
/// Trine Schønfeldt

Guest researcher

/ Elisa Martini

Bachelor and master's students

/ Guðrún Nanna Árnadóttir
// Ziao Zeng

Lab managers, technicians and specialists


/// Christina Agerbeck
/// Ditte Viborg Petersen
/// Fie Bendix Thomsen
/// Gitte Stæhr Hemmingsen
/// Helene Meyer Martin
/ Julie Weber Friis
/// Maja Søberg Udsen
/// Majken Kjær

/// Marta Madacsi
/// M Rodrigues de Carvalho
Bronze
/ Nikolaj Menne Bonefeld
/// Rasmus Borryng Klitgaard
/ Rebecca Kitt Davidson
Lohmann
/// Rikke Juul Wittrup
/ Sana Ahmed
// Sebastian Nuno
Bischofberger

Administration

/// Bitten Dalsgaard
// Charlotte Malassé
// Nils Erik Samdal
// Stine Kloppenborg

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LEO Foundation
Skin Immunology
Research Center

ADDRESS Blegdamsvej 3b
2200 Copenhagen N
Denmark

EMAIL sic@sund.ku.dk

PHONE +45 35 33 03 50

WEB sic.ku.dk

TWITTER @skinucph