

Annual Activity Report 2020

LEO Foundation
Skin Immunology
Research Center



UNIVERSITY OF COPENHAGEN

Contents

Introduction	3
Report from the Executive Director	4
Report from the Dean	5
2020 at a glance	6
Welcome to Professor Liv Eidsmo as Executive Director	7
T cell biology and skin inflammation	8
Skin inflammation and cancer	10
Molecular inflammation and cancer	12
Translational and clinical research	14
Single-cell RNA-sequencing projects	18
Education and career development	20
Funding and awards	27
Organisation and governance	28
Outreach and communication	30
Scientific output	32
Full staff list	35



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 the schoolchildren 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 becoming better understood. 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 and advance basic and clinical scientific approaches to skin disease and develop future leaders in the field, at the same time increasing knowledge and awareness of skin and skin diseases among medical professionals, patients and 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 Research Center will become a world-leading centre 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



Group Leader and Professor Charlotte Menné Bonefeld is the acting Executive Director of SIC.

Report from the Executive Director

2020 has been a special and unexpected year for all of us. The COVID-19 pandemic caused an unprecedented lockdown of our campus areas, greatly limiting our mobility and options for interactions, both internally and with the outside world. Naturally, the circumstances of the pandemic have meant major changes and adaptations to the plans we had for the year. But I am immensely proud of how we have succeeded in making the best of the situation. We managed to use the lockdown period to read up on important breakthroughs in immunological skin research from around the world. We wrote and published our own exciting journal articles. We took the leap to develop high-quality online teaching. And we took advantage of the highly skilled experts in skin and inflammation located throughout Denmark to put together an inspirational external seminar series.

The year has called for a sharpening of our attention to the activities and initiatives that mattered most to ensure continuous advances and scientific coherence at SIC. As soon as the doors opened slightly, we were quick to resume critical laboratory activity, which allowed our research groups to proceed with their projects, and we were able to take onboard several new PhD students for projects that had been on the drawing board before the pandemic became a reality. Importantly, we were able to welcome Professor Mads Gyrd-Hansen from the Ludwig Cancer Research at the University of Oxford as our newly recruited PI and Group Leader.

These activities and initiatives contribute to making 2020 a year we can look back at with a great sense of accomplishment, and I hope that throughout this report, our readers will recognise the important additions to our growing portfolio of projects and expertise that will allow us to make new discoveries within inflammatory skin diseases.

I would like to take this opportunity to thank everyone at SIC for your extraordinary efforts in the past year. At the time this is written, the University of Copenhagen and Denmark at large are once again subject to extensive restrictions due to the pandemic. Looking into the New Year, our approach is optimistic, yet realistic, as we acknowledge that in the coming months, we will still have to draw on our abilities to adapt our plans and be creative under challenging circumstances. I am confident that, together, we will continue to come up with the best possible solutions to move ahead.

2021 will also be the year where I hand over the leadership responsibility of SIC to our incoming Executive Director, Professor Liv Eidsmo. It has been the greatest privilege to be allowed to contribute to SIC's development – from the early consolidation stage to a place where we are now able to act out the Center's mission each day through our ambitious research projects and engaged teams. As we have gotten to know Liv Eidsmo, I find it very gratifying that she will continue to grow the Center in an inclusive, ambitious and spirited manner. We are all looking very much forward to supporting the Center and taking an active part in the next chapter of its lifetime. ✓



Ulla Wewer is Dean of the Faculty of Health and Medical Sciences, University of Copenhagen.

Report from the Dean

At no point in our lifetime has the need for excellence in research been more evident than in the past year. Health and medical sciences are on the agenda as never before, both as an answer to the perils of a pandemic and as a solution to the health challenges of our time, including those of precision medicine.

From the earliest stage at the LEO Foundation Skin Immunology Research Center (SIC) we have considered strategic recruitment of top international scientists as the key catalyst to achieving our goals of excellence, novelty and growth. Our goal is to add to the existing pool of expertise in skin immunology by increasing the number of excellent research groups. And I am delighted to report a significant success in this regard: We have been able to attract Professor Liv Eidsmo who is coming from Karolinska Institutet as new Group Leader and Executive Director of SIC and Professor Mads Gyrd-Hansen who is coming from Oxford University as new Group Leader. Both bring distinct skill sets and ideas that will supplement our existing groups in highly complementary ways. Further recruitments to the core group of PIs are planned for the near future. This important expansion of know-how allows SIC to further blossom and live up to the full potential of its unique platform. It will also add to the potential for partnerships across our Faculty and the utilisation of the translational capacities of our strong clinical network.

My expectations for SIC are high and with the many bright people and key collaborators, novel ideas and high-end technologies, I see SIC unravel the key questions in some of the world's most widespread immunological skin conditions through an ambitious collaborative, basic, translational, clinical and multi-disciplinary mindset. I also expect us to disseminate our discoveries to peers, the public and decision-makers. In the past year in particular, SIC has succeeded in digitally inviting the general public into the 'engine rooms' of our investigations as a way to convey the striking complexity and impact of modern skin disease research. Furthermore, SIC has taken giant leaps in incorporating high-end technologies and methods such as the new ground-breaking single-cell sequencing facility and proteomics approaches to carrying out detailed studies of individual cell expression profiles. This allows a much deeper understanding of the mechanisms and interplays of the immune system that can cause disease.

In closing, I believe that 2021 will become a new milestone in SIC's development. Although the Center's vision has always been crystal clear, we now see how SIC has truly established its own profile and direction for the future. I am eager to see our shared investments ripen into remarkable results for the benefit of the scientific community and patients around the world. /

2020 at a glance



FEBRUARY

SIC's first peer-reviewed article of the year was published in Journal of Dermatological Science.

See the full list of publications on page 33.

APRIL

SIC was awarded a BRIDGE Translational Excellence Programme Fellowship. The BRIDGE Fellowship was one of six new external research grants awarded to the SIC research groups this year.

Read about more new translational and clinical research projects on page 14.

See the full list of new external research grants on page 27.



MAY

The explanatory behind-the-research article *'The Skin – the body's largest organ and defence system'* was launched and enjoyed great exposure to the general public and stakeholders.

Read more about SIC's communication activities on page 30.

JUNE

SIC researchers ran the first pilot experiments on the new single-cell sequencing facility.

Read more about SIC's planned projects revolving around the single-cell RNA-sequencing technology on page 18.



AUGUST

Four new PhD students financed by the SIC grant were enrolled.

Read more about selected PhD projects in the *'Education and Career Development'* section on pages 20-26.

OCTOBER

Professor Mads Gyrd-Hansen took up his position as new Group Leader and core member PI.

Read more about the research group on page 12.

Read more about the role of SIC's core member PIs in the *'Organisation and Governance'* section on pages 28-29.



DECEMBER

SIC announced the recruitment of Professor Liv Eidsmo as new Executive Director.

Read more about Liv Eidsmo and her plans for SIC on the right-hand side.



Liv Eidsmo began her career as a MD-PhD student at Karolinska Institutet and Karolinska University Hospital. After that, she moved to a postdoc position at the University of Melbourne in Australia. She returned to Sweden to start up her own lab at the Center for Molecular Medicine (CMM) at Karolinska Institutet in parallel to clinical training in dermatology at Karolinska University Hospital.

Liv Eidsmo's research group at SIC will focus on how T cells residing in the skin drive local recurrence of diseases such as psoriasis and vitiligo.

Liv Eidsmo is newly appointed Professor in Translational Skin Immunology at the University of Copenhagen. She takes up the position as Executive Director of SIC in September 2021.

Welcome to Professor Liv Eidsmo as Executive Director

Liv Eidsmo from Karolinska Institutet has been recruited as Executive Director at SIC and appointed Professor at the University of Copenhagen. Her ambition is to tackle the big challenges in skin immunology by strengthening the collaboration between the basic and clinical research and thus creating a leading international centre for skin research.

Skin immunology research requires a strong connection between basic research and clinical dermatology. Based on an intensive international search for the Center's new permanent Executive Director, Liv Eidsmo was identified as the ideal candidate to meet this demand. Liv Eidsmo brings along extensive experience as an internationally recognised researcher and clinician, and her international network within skin immunology and dermatology will be an important asset for both the Center and the Faculty. She is further recognised for her demonstrated visionary leadership and inclusive approach to colleagues and students which will help the Center to continue thriving.

In connection with the move to Copenhagen, Liv Eidsmo highlights the excellent scientific environment and high-end technological facilities at the University of Copenhagen as an optimal platform for the development of a centre of excellence in skin immunology. She also underlines the possibility and importance of seamless collaboration with established dermatology clinics in the Greater Copenhagen area as a major attraction in her new role.

Liv Eidsmo transitions into her professorship in 2021 and assumes the responsibility as Executive Director in September 2021. Her first stated priority is to recruit new talent that will complement the existing expertise and add synergy to the already strong faculty at SIC. /

T cell biology and skin inflammation

The T Cell Biology and Skin Inflammation Basic Research Group investigates T cell development, 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.

T lymphocytes (T cells) are key players in many inflammatory skin diseases. T cells are central in the adaptive immune system and are characterised by high specificity and immunological memory. The precursors of T cells originate in the bone marrow and develop into T cells in the thymus. The microenvironment in the thymus is central for the complex selection process needed for a precursor cell to develop into a naïve T cell. After finishing the developmental process in the thymus, the naïve T cells leave the thymus and start their recirculation between the blood and lymph. Naïve T cells are activated when encountering their specific antigens. Upon activation, T cells will start proliferating and differentiating into effector and memory T cells.

In our group, we investigate several aspects of T cell biology in connection with the skin: 1) the interplay between the skin, thymus and T cell development; 2) how different factors (e.g., vitamins, cytokines and hormones) affect T cell activation and differentiation and T cell responses in the skin; 3) the development and regulation of different subsets of epidermal T cells in healthy and inflamed skin; and 4) the immune response to both single contact allergen and mixtures of allergen.

In 2020, the focus of our group has been on understanding the role of different skin proteins in T cell development. Over the last years, it has become clear that the composition of epithelial cells in the thymus is more complex than previously thought. It has been shown that subsets of thymic epithelial cells express several proteins known to be expressed on keratinocytes. Our focus is on how loss-of-function mutations in the skin barrier proteins filaggrin and mattrin affect the microenvironment in the thymus, and how it affects T cell development. We have used several different techniques to investigate this, including 3D imaging of solvent cleared organs and single-cell sequencing. Our preliminary data suggest that loss-of-function in one of these proteins not only affects the expression of this specific protein, but also the expression of other skin-related proteins within the thymus. This has an impact on T cell development, leading to the development of T cells with an altered inflammatory phenotype. How this correlates with the development of skin inflammation will be investigated during the next few years.

PROFESSORS

- ✓ Charlotte Menné Bonefeld
- ✓ Carsten Geisler

ASSISTANT PROFESSORS AND POSTDOCS

- ✓ Anne-Sofie Østergaard Gadsbøll
- ✓ Mandy Menzel
- ✓ Martin Kongsbak-Wismann
- ✓ Mia Hamilton Jee

ASSOCIATED ASSISTANT PROFESSOR

- ✓ Beatrice Dyring-Andersen

PHD STUDENTS

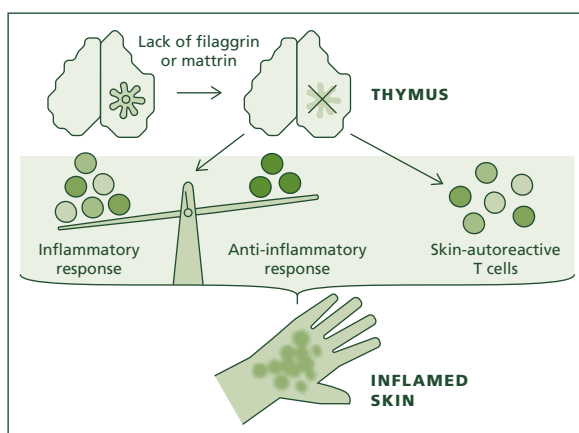
- ✓ Anna Kathrine Obelitz Rode
- ✓ Anders Boutrup Funch
- ✓ Daniel Villalba Lopez
- ✓ Fatima Abdul Hassan Al-Jaberi
- ✓ Kelvin Yeung
- ✓ Veronika Mraz

LAB MANAGERS AND TECHNICIANS

- ✓ Julie Weber Friis
- ✓ Louise Mørk



Thymic epithelial cells play a central role in T cell development. We hypothesise that lack of filaggrin and/or mattrin affect subsets of thymic epithelial cells which results in an altered T cell development leading to T cell driven skin inflammation.



In addition, we have investigated whether the glucagon-like peptide-1 receptor (GLP-1R) is expressed by T cells, and how vitamin D affects the expression of the GLP-1R and the production of IL-22. The GLP-1R is a G protein-coupled receptor, and activation of the GLP-1R leads to an increase in intracellular cAMP and Ca^{++} and promotes ERK1/2 signalling. GLP-1 stimulates insulin secretion and inhibits glucagon release. Several studies have indicated that GLP-1R agonists, in addition to their insulinotropic and anorexigenic effects, have anti-inflammatory effects. Our data indicate that the GLP-1R is expressed by regulatory T (Treg) cells, and that the anti-inflammatory role of GLP-

1R agonists may at least partially be ascribed to their activation of Treg cells. Interestingly, vitamin D significantly increases the expression level of the GLP-1R on T cells. In addition, we have characterised how vitamin D affects IL-22 production in T cells.

Finally, during the last few years, we and others have shown that exposure of the skin to contact allergens leads to a localised generation of epidermal-resident memory T cells. The epidermal-resident memory T cells mediate a rapid response within the local skin area upon re-exposure to the specific contact allergen. However, it is unknown if local skin memory just leads to a faster response, or if the response also differs immunologically from the response mediated by circulating memory T cells. We have investigated this using a mouse model and found that epidermal-resident memory T cells mediate a faster and enhanced response compared to the response mediated by circulating memory T cells. Furthermore, we found that the responses differed in chemokine profile and also in the effector cells recruited to the skin after exposure to the allergen. We will now analyse whether these findings translate to humans with allergic contact dermatitis and, if so, how this can be used in the development of new treatments for allergic contact dermatitis. /

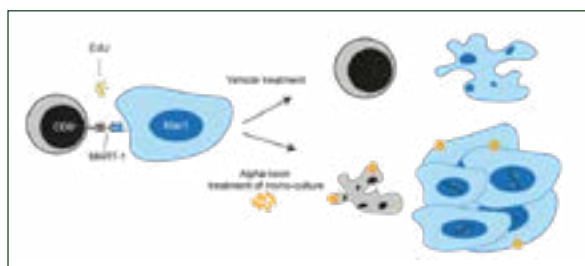
Skin inflammation and cancer

The Skin Inflammation and Cancer Basic Research Group focuses on elucidating the interplay between immunity, skin cells and the microbiota in order to understand what drives disease progression and resistance to treatment. The group is headed by Group Leader and Professor Anders Woetmann.

As inflammation damages the skin barrier, it paves the way for microbial colonisation that fuels more inflammation and disease progression. In 2020 in particular, we have investigated how disease mechanisms such as non-canonical functions of Janus kinases and aberrant metabolism contribute to malignant transformation of cutaneous T cells. Our hypothesis is that unusual, activated and localised JAK3 and overactive metabolism directly regulate proliferation and survival of malignant T cells in the skin. Targeting these pathways might open for new therapeutic intervention.

In addition, we have investigated how cutaneous microbiota affect the innate immune responses in the skin. Our hypothesis is that bacterially derived metabolites modulate the cutaneous innate immune system, and that this is important for maintaining tolerance and homeostasis in the skin under normal conditions. A deeper understanding of the crosstalk between microbiota, skin cells and the immune system is important for our understanding of cutaneous immunity.

We have continuously worked to identify novel T cell subpopulations believed to play a role in chronic skin inflammation and diseases such as psoriasis, e.g., IL-26 producing T cells. Our preliminary data suggest that several novel T cell subsets exist, and we hypothesise that they play important roles in the development and/or maintenance of inflammatory skin diseases.



We are currently working to establish novel analytic methods, including single-cell RNA-sequencing, in order to molecularly characterise and address the involvement of these novel T cell subsets in inflammatory skin diseases. Furthermore, we have started investigating the role of adipose stem cells (ASCs) and T cell oxidative stress in the regulation of inflammatory skin diseases. Our hypothesis is that ASCs are activated by inflammatory cytokines and play an important role in dampening the inflammation, and that they can therefore be used to treat inflammatory skin diseases. Oxidative stress in T cells modulates cytokine production and drives skin inflammation. Understanding how oxidative stress modulates T cell activation and function will allow for identification of novel therapeutic targets for treatment of T cell driven inflammatory skin diseases.

We have achieved a number of important results this year. We have discovered that Staphylococcus aureus (SA)-derived alpha toxin targets healthy cytotoxic CD8+ T cells, but spares malignant T cells, and that SA superantigens induce a regulatory phenotype in malignant T cells, allowing escape from anti-tumour immunity. Moreover, we have identified molecular mechanisms that modulate cytokine production in malignant T cells towards a Th2 profile. In the coming period, we will build on these results to explore treatment targets and principles in order to understand how aberrant metabolism and environmental factors such as bacteria-derived toxins influence malignant survival and proliferation. /

Staphylococcal alpha-toxin kills anti-tumour cytotoxic CD8+ T cells which in turn allows for continued proliferation of cutaneous T cell lymphoma cancer T cells (Mac1).



PROFESSORS

- / Anders Woetmann
- / Niels Ødum

ASSOCIATE PROFESSOR

- / Thorbjørn Frej Krejsgaard

ASSISTANT PROFESSORS AND POSTDOCS

- / Andreas Willerslev-Olsen
- / Emil Marek Heymans Pallesen
- / Nicolai Skovbjerg Arildsen
- / Tea Kirkegaard Nielsen
- / Terkild Brink Buus

PHD STUDENTS

- / Chella Krishna Vadivel
- / Cheng Chi
- / Eileen Donohue Wedge
- / Katharina Wörzner

- / Lisa Harth
- / Lukas Peiffer
- / Maria Gluud Grøndahl
- / Maria Teresa Martin Monreal
- / Marina Ramírez Galera
- / Martin Rich Javadi Namini
- / Minna Kaarina Lund Tiirikainen
- / Oliver Krigslund
- / Shayne Lavondua Ford

GUEST RESEARCHERS

- / Marina Passos Torrealba
- / Sara Torres Rusillo

LAB MANAGERS, TECHNICIANS AND ASSISTANTS

- / Cecilie Hald Andersen
- / Nadja Thisted Sauerberg
- / Sana Ahmad



Molecular immunology and inflammation

The Molecular Immunology and Inflammation Group focuses on understanding the fundamental processes that control immune responses, with particular focus on molecular mechanisms that are governing inflammatory signalling, innate immunity and other host-defence processes. Through this, 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 in September 2020 with the recruitment of Professor Mads Gyrd-Hansen from the University of Oxford.



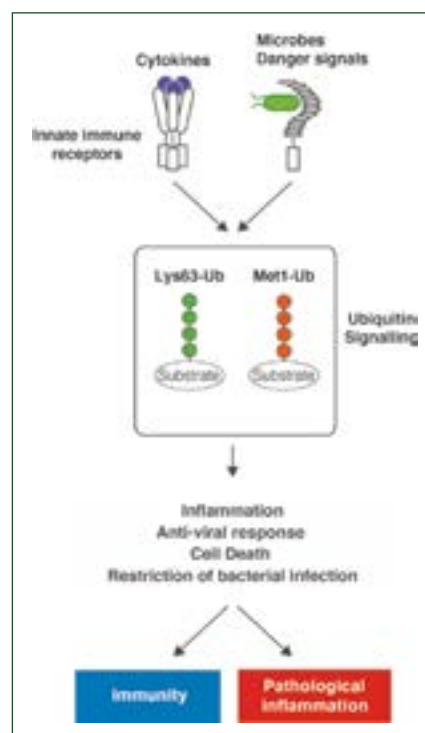
Our research focuses on understanding the processes that control immune responses, with particular focus on innate immune responses. The group studies molecular mechanisms governing inflammatory signalling and other host-defence processes and has a keen interest in the ubiquitin system which plays a central role in regulating inflammation and immune responses in the skin, gastrointestinal tract and other tissues/organs. Through this, we aim to understand the molecular events that on one hand protect against invading pathogens and tissue damage, but on the other hand contribute to chronic inflammation, autoimmunity and tumour development.

The modification of proteins with ubiquitin – termed ubiquitination – is essential for signalling by immune receptors, including pathogen-sensing pattern recognition receptors such as Toll-like and NOD-like receptors and cytokine receptors such as TNF receptor 1, IL-1 β receptor and IL-17 receptor. Signalling by these receptors is critical for the function of both immune and non-immune cells and plays a critical role in orchestrating inflammatory responses. Upon activation of immune receptors, ubiquitin is assembled into polymeric ubiquitin chains by ubiquitin E3 ligases and is disassembled by deubiquitinases. Depending on how they are assembled, these chains 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 (termed Lys63-Ub and Met1-Ub in the illustration) function as essential signalling scaffolds in pro-inflammatory and innate immune signalling.

Met1-linked ubiquitin chains have emerged as hugely important in regulating inflammation and immunity in animal models as well as in humans, and genetic mutations impacting the cellular machinery that regulates these ubiquitin chains give rise to serious pathological inflammatory conditions, including dermatitis and cutaneous tumours. Over the last 7-8 years, we have contributed to the

molecular characterisation of the core machinery that generates and disassembles Met1-linked ubiquitin. On this basis, Group Leader Mads Gyrd-Hansen has been awarded a 7-year Novo Nordisk Foundation Young Investigator Award to study the regulation of Met1-linked ubiquitin chains and its impact on the immune function at SIC. Leveraging our investigations of fundamental, regulatory mechanisms, we will explore how Met1-linked ubiquitin chains specifically affect immune responses and inflammation in the skin. Through collaborations with the other research groups at SIC, we aim to elucidate novel mechanisms that contribute to maintaining skin homeostasis and that ultimately may reveal novel molecular targets for future therapies.

The Molecular Immunology and Inflammation Group is in the establishment phase, i.e., we are recruiting staff and transferring mice lines and research reagents from the Gyrd-Hansen research group in Oxford. The SIC group currently consists of an assistant professor, a postdoc and a research assistant. The main goals for 2021 are to recruit 3-4 additional staff to the group, to relocate research activities from the Oxford group and to initiate new research projects. The research group at the University of Oxford will close down by 1 December 2021 after which Mads Gyrd-Hansen will be heading the Molecular Immunology and Inflammation Group on a full-time basis in Copenhagen. /



Ubiquitin signalling in the innate immune response.

PROFESSOR

/ Mads Gyrd-Hansen

ASSISTANT PROFESSORS AND POSTDOCS

/ Berthe Katrine Fiil

/ John Rizk

RESEARCH ASSISTANT

/ Frederik Timmermann

Translational and clinical research

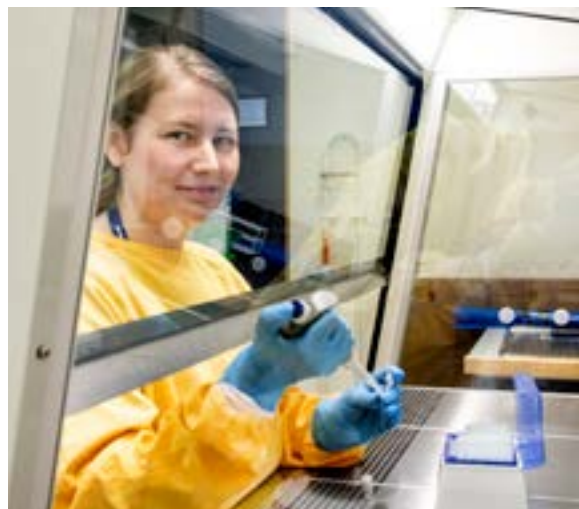
SIC is strongly committed to integrating the basic research groups at the SIC headquarters at the Faculty of Health and Medical Sciences with translational and clinical research forces at Danish and international hospitals. On these pages, we are highlighting new translational and clinical research projects that have emerged from the 'Team Science Concept', as adapted by basic and clinical researchers at and associated with SIC. This approach translates basic discoveries to the patients, and it ensures that observations and questions arising in the clinic are referred back to the laboratory.

ALLERGY AS A POTENTIAL CAUSE OF IMPAIRED IMMUNITY TO BACTERIAL INFECTIONS IN PATIENTS SUFFERING FROM ASTHMA AND ATOPIC DERMATITIS

Asthma affects more than 200 million people worldwide. The majority of cases is characterised by an atopic component, defined as a heightened immune response to one or more common aeroallergens or food allergens. The first manifestation of atopy is often atopic dermatitis which may then progress to food allergies, allergic rhinitis and allergic asthma – a process called 'atopic march'. Studies have found that children with atopic dermatitis are more prone to developing atopic asthma, and that the likelihood of developing asthma increases with increasing eczema severity. These findings identify the skin as an important route of allergen exposure and sensitisation that might contribute to the development of allergic asthma.

This BRIDGE fellowship investigates research questions that stem from recent scientific observations that patients suffering from severe asthma are at a higher-than-normal risk of being prescribed antibiotics for respiratory infections caused by bacteria. Moreover, it has been observed that these patients seem to benefit from allergic immunotherapy, leading to fewer infections and a reduced need for antibiotic treatment. However, researchers do not yet know which immunotherapy mechanisms lead to a better response to bacteria. The aim is thus to unravel molecular and immunological mechanisms that link atopy to susceptibility to bacterial infection. The expectation is that the findings can be used for patient stratification to identify patient groups particularly at risk of contracting infections and to identify molecular targets for novel treatment approaches to atopic diseases.

Menzel has a PhD in Biomedicine from Lund University. She was recruited as postdoctoral fellow as part of the BRIDGE Translational Excellence Programme in autumn 2020 to work on the project investigating impaired immunity to bacterial infections in patients suffering from asthma and atopic dermatitis.





The fellowship builds on a very strong translational network. With expertise in asthma and immunology of the skin, respectively, Clinical Professor Celeste Porsbjerg, Bispebjerg and Frederiksberg Hospital, and Professor Charlotte Menné Bonefeld, SIC, make up the mentorship team for research fellow Mandy Menzel. The clinical trials in the project will be performed at the Respiratory Research Unit at Bispebjerg Hospital, which has extensive experience in mechanistic studies of asthma. SIC provides high-end facilities for in vitro and molecular biology analyses and extensive knowledge on allergies and immunological responses in the skin. Parts of the study involving bronchial epithelial cell biology will be conducted in the lab of collaborator Professor Lena Uller at Lund University. /

BRIDGE – TRANSLATIONAL EXCELLENCE PROGRAMME

The postdoctoral BRIDGE fellowships in translational medicine are funded by the Novo Nordisk Foundation and offered to selected researchers working on translational research projects at the University of Copenhagen. Fellows apply new discoveries and technologies from biomedical research to the clinical environment or to the life science industry, thus bridging the gaps between research and medical treatment.

THE IMMUNOSUPPRESSIVE ROLE OF ADIPOSE-DERIVED STEM CELLS IN INFLAMMATORY SKIN DISEASES

Inflammatory skin diseases such as psoriasis and atopic dermatitis (AD) are caused by a complex interaction between immune and skin cells via the release of soluble mediators. In the case of psoriasis, the interplay between keratinocytes and different T cell subsets such as Th1, Th2, Th17, CD8+T and Tregs has – in combination with the presence of pro-inflammatory cytokines such as IFN- γ , IL-22, TNF- α , IL-23, and IL-17 – been recognised as a key pathophysiological mechanism leading to self-perpetuating inflammation and clinical manifestations. Of note, despite the increased disease understanding accumulated during the last decade, the aetiology of skin diseases remains unknown. Current therapies targeting pro-inflammatory cytokines (i.e., biologicals) in combination with conventional treatments (i.e., glucocorticosteroids) ameliorate the symptoms and reduce morbidity, but offer no cure. Therefore, new therapeutic approaches are mandatory in order to improve the life of patients with skin diseases. At the forefront is adipose-derived stem cell (ASCs)-based therapy, which is clinically promising due to its high immunomodulatory and anti-inflammatory potential.

Adipose-derived stem cells are mesenchymal stem cells (MSCs) isolated from adipose tissue. MSCs are multipotent stromal-derived non-hematopoietic progenitor cells that reside in and can be isolated from various tissues of adult and neonatal origin, including, among others, adipose tissue, bone marrow or cord blood. MSCs are of great interest due to their immunomodulatory properties. Firstly, MSCs are hypo-immunogenic cells because of their low expression levels of major histocompatibility complex (MHC) class I molecules, the lack of MHC-II as well as co-stimulatory molecules like CD80, CD 86, and CD40. This enables MSCs to be used as an allogenic therapy without potential risks for immune rejection. Secondly, MSCs affect both the innate and the adaptive immune systems. Interestingly, MSCs can inhibit the differentiation of monocytes into myeloid dendritic cells and promote an M2-like phenotype. Moreover, MSCs suppress T cell proliferation while promoting differentiation into Tregs. In addition, MSCs have a direct effect on B cells, inhibiting their proliferation, plasma cell differentiation and chemotaxis.

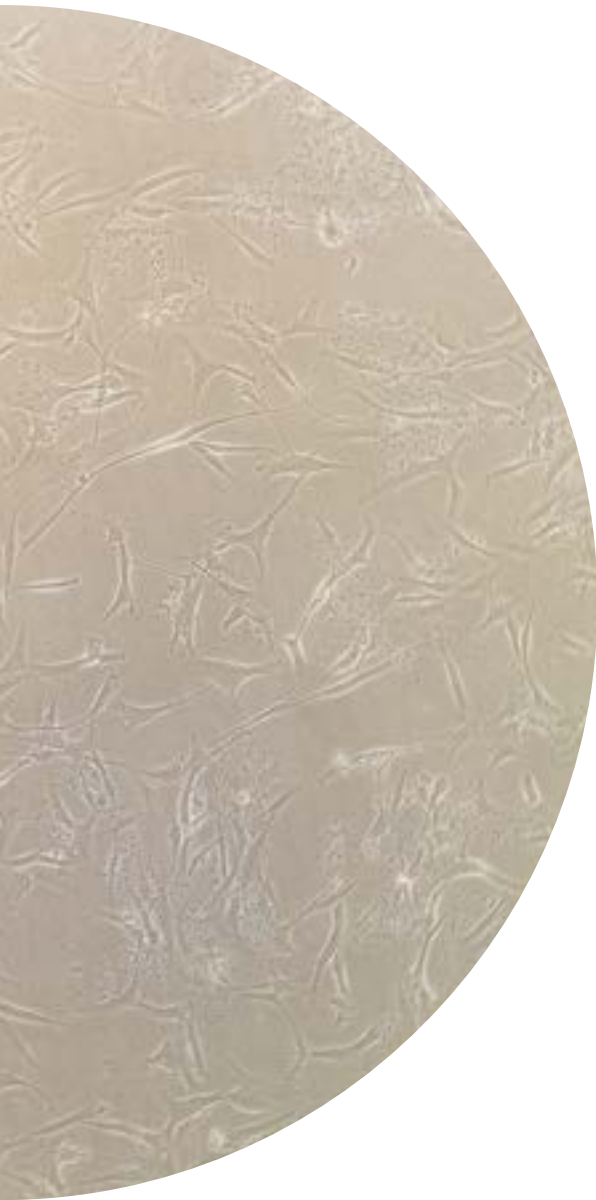
Considering these properties, it is not surprising to find an increasing large number of MSCs-based

clinical trials for many different immune disorders. Of note, the therapeutical potential of ASCs is under clinical investigation in various inflammatory and autoimmune diseases, but not in inflammatory skin diseases. Hence, the aim of our study is to elucidate the feasibility of ASCs as a new local skin inflammation treatment. To tackle this aim, we have already produced preliminary fundamental RNA-sequencing data that enable us to identify expression profiles of ASCs at the different stages during culture, and we intend to use it to monitor and confirm the quality of our ASCs culture and differentiation protocol. Moreover, these data will enable us to identify ASCs biomarkers to use in skin biopsies obtained from healthy as well as various inflammatory skin conditions. We also plan to characterise the molecular features, including key mediators in the interplay between ASCs and immune cells, elucidate ASCs' therapeutic potential in ex vivo inflammatory skin models and thoroughly profile and compare the ASCs population in normal and inflamed skin. Overall, the research project will provide a deeper understanding of the immune/stem cell axis as a new therapeutic target for inflammatory skin diseases.

The project is established in close collaboration between Professor Anders Woetmann, SIC, and Postdoc Jesper D. Svalgaard from the Copenhagen-based company Stemform which provides in-depth expertise into ASCs and access to adipose tissue. /



Marina Ramírez Galera started her career as an Associate Scientist in the pharmaceutical industry before taking on the position as a PhD student, studying the immunosuppressive role of adipose-derived stem cells at SIC.



Therapy based on adipose-derived stem cells has a high immunomodulatory and anti-inflammatory potential and is thus a promising target in the treatment of inflammatory skin diseases.

Kelvin Yeung finalised his training as a medical doctor before taking on studies in epidermal-resident memory CD8⁺ T cells in allergic contact dermatitis as a PhD student in the SIC/CAG collaboration.

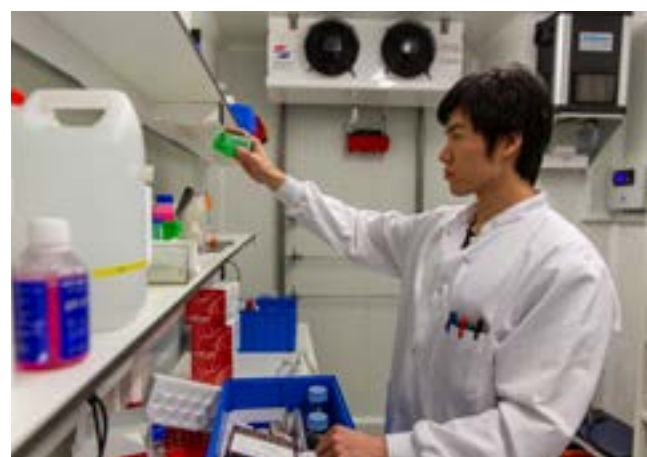
THE ROLE OF IL-1 β IN THE MAINTENANCE AND FUNCTION OF EPIDERMAL-RESIDENT MEMORY CD8⁺ T CELLS IN ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) is an inflammatory skin disease caused by cutaneous contact with an allergen, inducing a cell-mediated type 4 hypersensitivity immune reaction. Contact allergens are low molecular weight chemicals, e.g., metals, fragrances and preservatives that can modify self-proteins in our skin in such a way that these proteins become immunogenic.

The immune response induced by contact allergens can primarily be divided into two crucial phases: 1) the sensitisation phase and 2) the elicitation phase. During the sensitisation phase, allergen-specific naive T cells are activated, leading to the generation of allergen-specific memory T cells. The exposed individual is now said to be sensitised. Re-exposure to the allergen induces the elicitation phase by activation of allergen-specific memory T cells.

ACD is clinically characterised by erythema, pruritus, oedema, blistering, thickening and scaling skin. The estimated prevalence of ACD to at least one contact allergen in North America and Northern Europe is 21.2% and, in recent years, the incidence of ACD has been steadily increasing in correlation with an increasing number of environmental detergents.

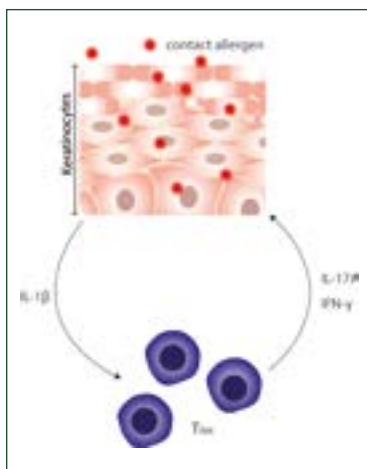
Although local T cell memory plays a central role in inflammatory skin diseases, the maintenance and function of epidermal-resident memory CD8⁺ T cells are still unclear. However, prior studies have shown IL-1 β to be a key cytokine in murine allergic contact dermatitis models. Our aim is to investigate if there is a positive feedback-loop between keratinocytes and epidermal-resident memory CD8⁺ T cells. Our hypothesis is that the T cells produce IFN- β and



IL-17A which induce an increased production of IL-1 β from the keratinocytes. The IL-1 β enhances the maintenance and the pathological effector function epidermal-resident memory CD8+ T cells, which then stimulates keratinocytes to produce IL-1 β . This will be studied through murine models and clinical trials.

The current treatment regimen of ACD consists of identification and elimination of the eliciting contact allergen in combination with topical steroids and moisturising creams, in order to alleviate and reduce clinical symptoms. Phototherapy and photo chemotherapy can be a complementary treatment for ACD patients resistant to topical steroid treatment. In more severe cases of ACD, systemic immunosuppressant therapy may be needed such as glucocorticoids, disease modifying anti-rheumatic drugs and vitamin A derivatives. Systemic therapy has serious side effects, and not all patients with ACD respond well to the presently available treatments. Therefore, there is a need to explore alternative forms of treatment of ACD. A closer understanding of the role of IL-1 β in the maintenance and function of epidermal-resident memory CD8+ T cells might potentially lead to the development of novel treatments for allergic contact dermatitis, and also for psoriasis, atopic dermatitis and other inflammatory skin conditions.

The project is integrated into SIC and the Clinical Academic Group (CAG) in Allergy. As part of the Greater Copenhagen Health Science Partners collaboration, the CAG strongly supports collaboration between basic and clinical research at hospitals and universities in the region. The PhD project is supervised by Clinical Professor Lone Skov, Herlev and Gentofte Hospital, and Professor Charlotte Menné Bonefeld, SIC. /



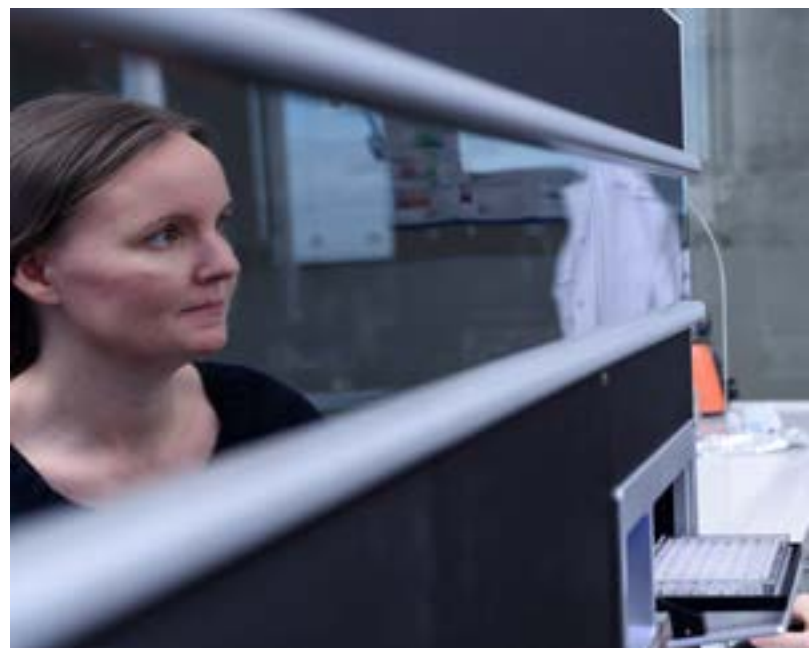
The PhD study investigates if there is a positive feedback loop between keratinocytes and epidermal-resident memory CD8+ T cells.

Single-cell RNA

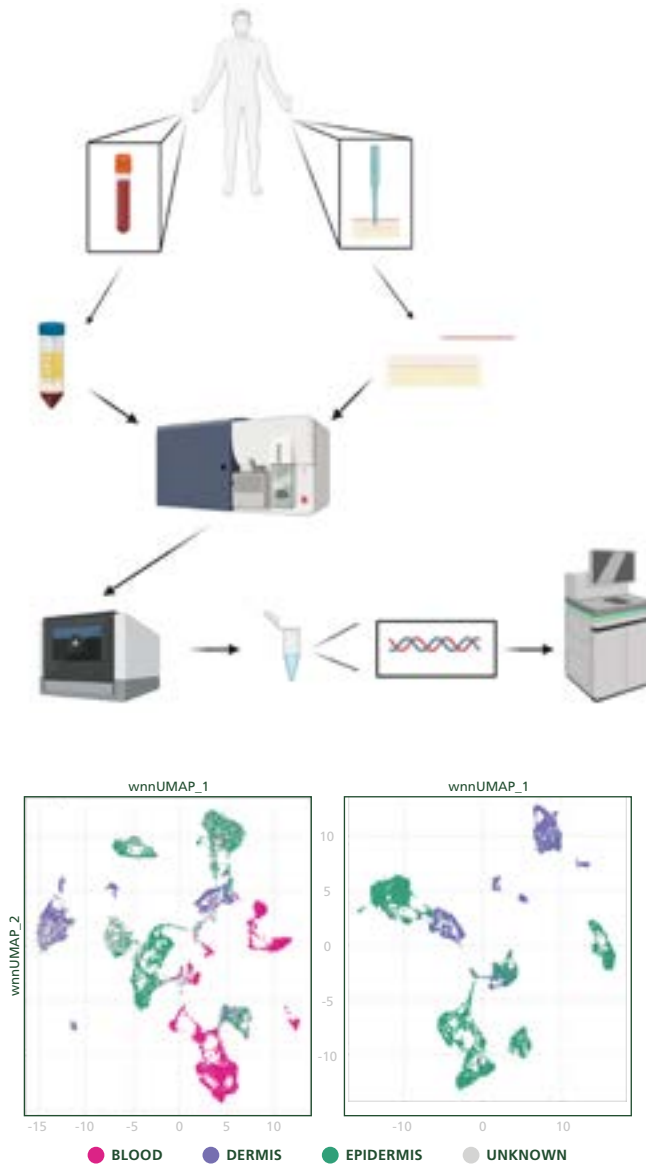
In 2019, SIC was awarded a strategic add-on grant of DKK 15.3 million by the LEO Foundation to build a state-of-the-art facility for single-cell sequencing. The first pilot experiments were conducted in the facility during summer 2020 with successful preliminary results.

Single-cell sequencing is a valuable tool to increase our knowledge about the cellular response that is driving inflammatory skin diseases. Traditional methods to measure gene transcripts, e.g., 'bulk' RNA-sequencing or gene expression microarrays measure the average expression within the sample, e.g., within the skin biopsy, but these methods do not distinguish the expression within individual cells in the sample. In contrast, single-cell RNA-sequencing offers the ability to analyse genome-wide transcriptional profiles on the single cell level. This means that it is possible to identify each individual cell expression profile in the sample, even if the cells only constitute a minor fraction of the total sample. In this way, the technology offers unique opportunities for getting a more precise understanding of disease mechanisms and heterogeneity.

Since the opening of the advanced facility, SIC has allocated resources for 13 different projects revolving around single-cell RNA-sequencing across the research groups. In preparation for these projects, we have worked continuously to optimise the protocols for purification of different cellular subsets from the skin and to be able to identify rare T cell populations. As our primary focus is the



-sequencing projects



immune cells and, in particular, T cell populations, we will elucidate the V(D)J transcripts from both T cell receptors (TCR $\alpha\beta$ and $\gamma\delta$) in the planned projects. Furthermore, we add an antibody panel containing up to 92 different antibodies to enhance the information level obtained from the experimental setups. The antibodies provide us with the surface protein levels, which particularly is an advantage for the immune cells containing a low amount of mRNA, e.g., CD4 T cells.

By using single-cell RNA-sequencing in our first projects, we aim to investigate the expression profile of different subsets of cells within the skin to determine any difference between the various anatomic locations. This can help us explain why some inflammatory skin diseases have a tendency to be localised so specifically. Furthermore, we plan to determine the cellular expression profile in different inflammatory skin diseases and how various known and experimental treatments affect the expression profile of subsets of key-cellular players in various skin diseases. ✓

Workflow from purification of cells from blood and punch biopsies, to FACS cell sorting and through the 10X platform ending in sequencing, here using the NovaSeq 6000 system. The analysis of the data can, for example, end in a visualization via a umap plot, here showing data from blood and different compartments of the skin.



Lab Technician Julie Weber Friis and colleagues across the research groups have worked intensively to optimise protocols for experiments to be run in the new single-cell sequencing facility.

Education and career development

SIC invests heavily in the training of the next generation of immunologists in an ambitious learning environment. On these pages, we present SIC's main educational activities that aim to prepare students for auspicious international careers within academia and the life science industry. We also highlight four recently launched and promising PhD projects, made possible through the SIC grant.

PRE- AND POSTGRADUATE EDUCATION

SIC provides training in basic and advanced immunological skills within a range of educational programmes in health and medical sciences offered at the Faculty. At the bachelor's and master's degree level, SIC's researchers are particularly involved with the Master of Science in Immunology and Inflammation. The Master is unique in Europe as it is the only Master in Immunology taught in English in continental Europe, making it a highly coveted international programme. Each year, the programme enrolls approx. 30 students of more than 10 different nationalities. At the postgraduate level, the majority of SIC's PhD students are enrolled in the Immunology and Infectious Diseases graduate school programme where SIC's researchers provide high-quality training and supervision. Group Leaders Anders Woetmann and Charlotte Menné Bonefeld at SIC lead these advanced pre- and postgraduate programmes as Head of Studies and Head of Graduate Programme, respectively. ✓

IN 2020, SIC RESEARCHERS:

- ✓ Delivered 114 teaching hours
- ✓ Conducted 257 exams at bachelor's and master's degree level
- ✓ Supervised 11 bachelor's and master's thesis students
- ✓ Supervised 21 PhD students

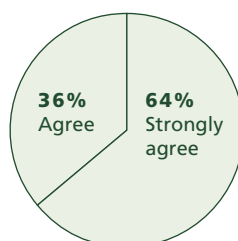
TOP THREE TEACHING PROGRAMMES

- 1 Immunology and Inflammation
- 2 Medicine
- 3 Human Biology

MASTER'S COURSE IN SKIN IMMUNOLOGY

As part of the Center's educational strategy, SIC has developed a new elective course in skin immunology offered to students at the Master in Immunology and Inflammation programme. The course was conducted in spring 2020 for the first time. 22 students actively pursued this opportunity to learn and understand the immunology of the body's largest organ. A broad range of PhD students, postdocs and faculty members at SIC and ISIM contributed to the course together with several clinical collaborators, thus enabling us to cover both basic and clinical aspects of skin immunology and experimental methods in the study of skin immunology. The course starts with an overview of resident and recruited cells found in healthy and diseased skin, and this part of the course concludes with the creation of a model of the cellular composition in the skin. Next, the students are taught about different skin infections. The focus is on HPV, herpes simplex virus, *S. aureus*, cutibacterium acnes, scabies and mycobacteria leprae, and this part of the course ends with a skin infection quiz. Finally, different pathological conditions in the skin are discussed, i.e., wounding, cutaneous T cell lymphoma, atopic dermatitis, psoriasis, allergic contact dermatitis, pemphigus, cutaneous adverse drug reactions and Graft versus Host Disease.

"Overall, I benefitted greatly from this course"



0%
Disagree

0%
Strongly disagree

0%
Neither

0%
Not relevant

Student evaluation of learning outcomes of the Master's course in skin immunology.



Due to the COVID-19 situation, the course was changed to an online format this year with live-streamed lectures and digital teaching sessions. Fortunately, both students and teachers were constructive and supportive in creating the best possible learning outcomes. The course ended with an online exam, where the students performed very well and demonstrated a high level of knowledge within basic, experimental and clinical skin immunology. The students evaluated the course very positively, and we look forward to conducting the course again during the spring 2021 – hopefully this time with lectures and classroom teaching on campus. /

SIC provides training in basic and advanced immunological skills, covering a range of educational programmes within health and medical sciences. SIC's researchers also host and supervise students who are working on their thesis, at both bachelor's and master's degree level.

Photo: Adam Mørk for C.F. Møller.

YOUNG INVESTIGATOR NETWORK

The Young Investigator Network was established by early career researchers from SIC and clinical dermatological departments in the Copenhagen area in 2019. The network is a self-organising professional and social initiative that aims to expand the professional networks of its members and initiate interdisciplinary research activities with peers. Each member contributes with specialised skills, methodological expertise and unique access to data within their particular field of basic, translational and clinical skin and skin disease research. Members enjoy support from their respective PIs and departments and have an allocated budget to perform career development activities and explore the synergetic potentials in collaborations.

The network kicked off 2020 with an inspiring invited talk by world-renowned genetics scientist Eske Willerslev from the Globe Institute, University of Copenhagen, and a subsequent guided tour of the facilities available in SIC's laboratories in the Mærsk Tower. Although the options for traditional networking meetings have since been limited, members have utilised the bilateral connections established through the network to share knowledge and together set up experimental designs throughout the year. /

The Planning Group is responsible for planning and holding meetings in the Young Investigator Network. The Planning Group consists of representatives from each participating department.

SIC – T cell biology and inflammation group
Assistant Professor Martin Kongsbak-Wismann (Chair)

SIC – Skin inflammation and cancer group
Postdoc Emil Marek Heymans Pallesen

SIC – Molecular immunology and inflammation group
Assistant Professor Berthe Katrine Fiil

Zealand University Hospital, Roskilde
PhD student Pernille Lindsø Andersen

Bispebjerg and Frederiksberg Hospital
PhD student Jesper Grønholm Lund

Herlev and Gentofte Hospital
PhD Student Lise Gether

PhD degrees awarded in 2020



KATRINE YDERSTRÆDE BAUMANN

Thesis: *Microdialysis sampling of biomarkers from human ex vivo skin*

Next destination: PhD Katrine Yderstræde Baumann continues her academic career in the Danish life science industry.



LAURA MASSARENTI

Thesis: *Molecular and microbial links between rheumatoid arthritis, systemic lupus erythematosus and periodontitis*

Next destination: PhD Laura Massarenti continues her academic career in Denmark.



PER LARSSON

Thesis: *Multiple cellular pathways in cancer metastasis and targeted treatment strategies*

Next destination: PhD Per Larsson continues his academic career in Sweden.



MIA HAMILTON JEE

Thesis: *Skin and thymus connections – effects on T cell development*

Next destination: PhD Mia Hamilton Jee continues her academic career as a postdoc at SIC.

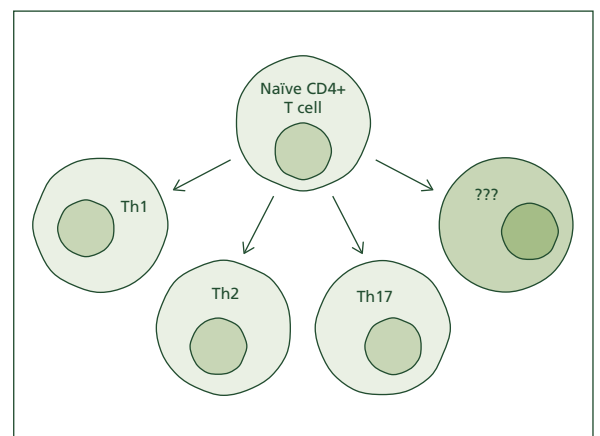
ROLE OF NOVEL T CELL SUBSETS IN THE CONTEXT OF PSORIASIS AND OTHER SKIN DISEASES



In the case of psoriasis, it has been generally accepted that the IL-23/Th17 axis is responsible for the symptoms and chronicity of the disease, however, there are still issues that need to be resolved. One of the issues is that people with psoriasis suffer from a higher rate of comorbidities such as metabolic and cardiovascular disease. Another issue is that biologic drugs for disrupting the IL-23/Th17 axis can be neutralised due to their inherent immunogenicity, which can render them ineffective over time. Furthermore, to our knowledge, there is no evidence that treatment with biologic drugs for psoriasis decrease the incidence of comorbid diseases. It would thus be beneficial if novel factors in the pathogenesis of psoriasis were identified as such information could open up the potential of understanding the mechanism behind the systemic nature of psoriasis and lead to small molecule therapeutics that are not subject to the pitfalls of biologic drugs (e.g., high cost and immunogenicity).

In this project we have identified production of a cytokine that has purportedly not been produced by T cells. Furthermore, single-cell RNA-sequencing and in situ hybridisation data have indicated that T cells producing the cytokine exist naturally in the T cell milieu of healthy people. In addition to identifying these cells, we have also identified several kinases within signal transduction pathways that can either stimulate or inhibit production of the cytokine when inhibited with small-molecule kinase inhibitors. Currently, we are about to launch an investigation into the function of the cytokine when produced in vivo by T cells. To do this, we will

Shayne Ford graduated from the Immunology and Inflammation Master's programme at the University of Copenhagen prior to taking on the position as PhD student to study the role of novel T cell subsets in the context of psoriasis and other skin diseases.



Discovery of a new subset of T cells – and intracellular targets which regulate production of its signature cytokine – could add to the toolbox of therapeutics for treatment of T cell mediated diseases.

begin by performing single-cell RNA-sequencing in 2021. The purpose of the upcoming experiments will be to further characterise this novel subset of cells and to expand our ability to identify members of the subset. The project is interesting because the discovery of a new subset of T cells – and intracellular targets which regulate the production of its signature cytokine – could add to the toolbox of therapeutics for treatment of diseases that are mediated by T cells. ✓

STRESS MOLECULES PLEXIN-B2 AND CXADR IN THE RESPONSE TO CONTACT ALLERGENS

The skin is the largest organ of the body. It forms an active barrier that provides the first line of defence against infections. Extensive crosstalk between the different cellular and microbial components of the skin regulates local immune responses to ensure efficient host defence, to maintain and restore homeostasis and to prevent chronic disease.

Allergic contact dermatitis (ACD) is a common inflammatory skin disease that causes considerable morbidity. Contact allergy is regarded as a delayed hypersensitivity reaction (type IV hypersensitivity), mediated by antigen-specific T cells. ACD is a disease with a complex pathophysiology. Nowadays, it is commonly prevented by avoidance of exposure to specific contact allergen or treated with corticosteroids or cyclosporine. Studies investigating precision therapeutics are thus crucial for the development of more specific treatments of ACD.

In this project, we are investigating two molecules, Plexin-B2 and coxsackievirus and adenovirus receptor (CXADR), that could potentially play important roles in the pathophysiology of ACD. Those molecules have been extensively studied in relation to several pathologies with an exception of ACD. Plexins constitute a family of transmembrane proteins that function in cell adhesion and are the predominant family of semaphorin receptors. A number of studies have demonstrated an important role for semaphorins in the immune system through interaction with plexins. CD100, also known as Semaphorin 4D, is one of the most well-characterised semaphorins on T cells. The interaction between CD100 and Plexin-B2 was shown to activate inflammasome, and the disruption of this axis was shown to exacerbate wound healing. The second molecule of interest, the CXADR, was first identified as a high-affinity receptor for coxsackie B viruses and adenoviruses and was subsequently shown to belong to the junction adhesion molecule (JAM) family. It is localised in tight junctions and along the lateral membrane of epithelial cells throughout the body. The junctional adhesion molecule-like protein (JAML) is a receptor for CXADR and is expressed on a variety of cells of the adaptive and innate immune systems, including neutrophils, monocytes and memory T cells. Previously, it was shown that interaction between CXADR and JAML in the skin leads to the proliferation of dendritic epidermal



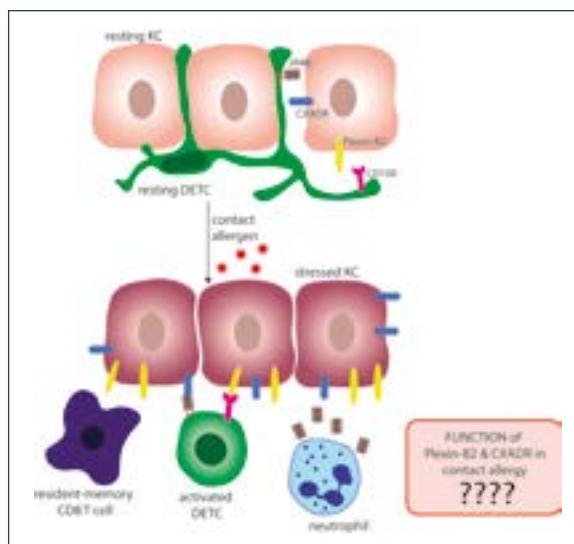
T cells (DETC) and therefore is crucial in modulating DETC responses. Interestingly, another study has shown that the JAML-CXADR interaction during the intestinal epithelial injury leads to a compromised barrier and inhibition of wound healing, through decreased epithelial proliferation.

The aim of this project is to elucidate the roles of Plexin-B2 and CXADR on keratinocytes (KC), following exposure to contact allergens. At first, we want to investigate how the expression of those molecules are affected by the contact allergen-stressed microenvironment in mouse and human skin. Furthermore, we want to investigate the effects of Plexin-B2 and CXADR on epidermal T cells in the sensitisation and elicitation phase of ACD.

Our preliminary data show that both Plexin-B2 and CXADR are up-regulated on contact allergen-stressed murine KC in vitro. Furthermore, our data indicate that Plexin-B2 is up-regulated in a dose-dependent and time-dependent manner in human epidermis from healthy donors following the treatment with contact allergen ex vivo.

A greater knowledge of the pathways involved in Plexin-B2-CD100 and CXADR-JAML interactions in ACD will not only allow us to understand the disease better, but might also contribute to the development of more specific treatments of ACD. /

As a PhD Student, Veronika Mraz studies the stress molecules Plexin-B2 and CXADR in the response to contact allergens. She is a graduate from the Immunology and Inflammation Masters' programme at the University of Copenhagen.

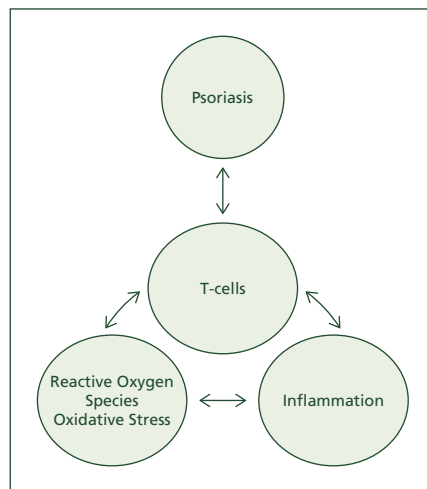


The project aims to elucidate the roles of Plexin-B2 and CXADR on keratinocytes (KC) following the exposure to contact allergens.

REACTIVE OXYGEN SPECIES IN CUTANEOUS T CELL IMMUNOLOGY

Reactive oxygen species (ROS) are small, reactive molecules derived from oxygen. For long, ROS has been thought of as nothing but toxic by-products of metabolic processes. However, it is becoming increasingly evident that ROS are important regulators of cellular signalling networks and thus are tightly fine-tuned and regulated by metabolic processes and powerful enzymatic and non-enzymatic antioxidant molecules. Adding to this, it has been found that environmental triggers such as exposure to sunlight, chemicals, chronic infections or inflammation can influence local levels of ROS.

Oxidative stress (OS) may be part of a vicious circle nurturing chronic or recurrent inflammatory conditions.

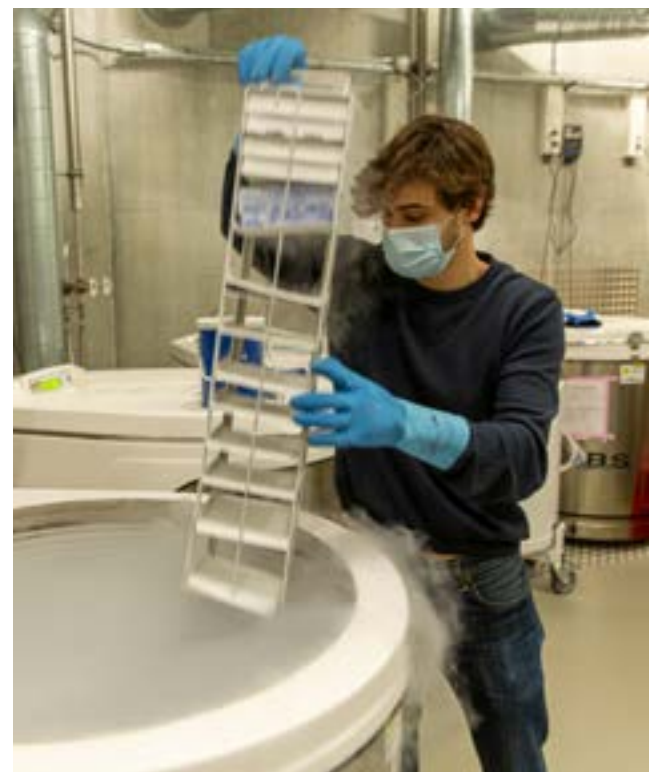


These findings have spurred a lot of research into ROS biology and the state of oxidative stress (OS) that arises in cells that are unable to balance either the production or the detoxification of ROS. Just as infections and inflammation can lead to ROS imbalances and OS, OS can, in turn, also lead to both dysregulation of cell signalling pathways, inflammation and ultimately cell death. Thus, OS may be part of a vicious circle, nurturing chronic or recurrent inflammatory conditions.

Of importance to the immune system, ROS have been found to be important signalling molecules in T cell receptor signalling and T cell activation, and it was thus reasonable to look for ROS perturbations in diseases involving T cells. Accordingly, numerous reports have documented that patients with benign inflammatory skin diseases such as psoriasis and atopic dermatitis display clear lesional and

systemic hallmarks of OS. Although accumulating evidence supports that OS may also contribute to the pathogenesis of these inflammatory skin diseases, the underlying mechanisms remain unclear. Part of the reason for the lacking knowledge is that, until recently, it has been challenging to distinguish between the various ROS, to quantify ROS and to pinpoint cellular location. However, new and more specific assays are emerging together with a fuller understanding of the sources of ROS which, together, should enable new insight.

The current project aims to take advantage of the established and emerging assays to further unravel mechanisms of ROS in skin and cutaneous T cells. This will be accomplished by obtaining and examining T cells from human skin as well as looking at full skin. Cells and skin will be subjected to ROS inducing and scavenging treatments prior to analysis by multi-colour flow cytometry, RNA-sequencing amongst others. Collectively, these experiments are expected to yield information on ROS effects on individual cell types and their interplay in the complex environment of the skin. Our expectation is that the project will lay the foundation for a better understanding of ROS and OS in cutaneous T cell immunology, concluding with the identification of new drug targets to treat psoriasis, atopic dermatitis and other T cell driven inflammatory diseases. /



Martin Namini finished his Master's degree in Pharmacy at the University of Copenhagen before taking on the position as PhD student to study reactive oxygen species (ROS) in cutaneous T cell immunology.

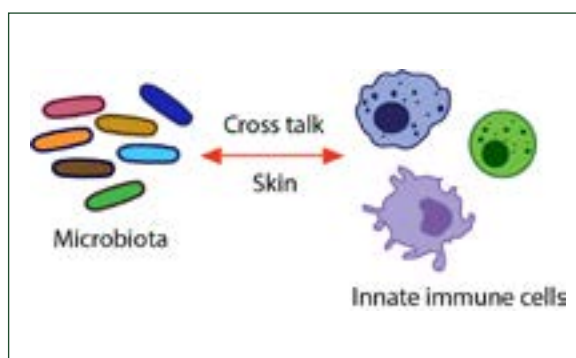
MODULATION OF CUTANEOUS INNATE IMMUNITY VIA HOST/SKIN MICROBIOME INTERACTIONS



The skin has the vitally important task to protect the body against constant threats from the outside world. Therefore, it harbours several factors that contribute to its ability to properly execute this function. One of these factors is the microbiota which seems contradictory as microorganisms form one of the daily threats the skin is supposed to protect the host from. Nonetheless, the microbiota are an indispensable part of the host as they are fundamental for the proper development of the immune system, which forms a second component of importance for the functioning of the skin. The immune system in turn carries the responsibility of keeping the microbiota within their boundaries.

This symbiosis evolved between the host and the microbiota hinges on communication with the innate immune system playing a central role in this dialogue. Over the years, it has become clear that a plethora of molecules is engaged in this dialogue, and the disruption of this crosstalk can lead to disease development. For a long time, it has been recognised that microbial-associated molecular patterns such as cell wall components and nucleic acid are a part of the communication with the innate immune system by interacting with pattern recognition receptors (PRRs). The initiation of these receptors creates a pro-inflammatory response that is important for tissue homeostasis and for keeping the microbiota in place. However, it is important to keep this pro-inflammatory environment at bay so it does not become detrimental for either parties. It is therefore not only critical to identify and understand which other components are

Lisa Harth studies host/skin microbiome interactions as a PhD student. She is a graduate from the Immunology and Inflammation Master's programme at the University of Copenhagen.



Investigations of how communication between skin innate immunity and microbiota is mediated will provide deeper insight into the way in which communication between microbiota and host regulates skin immunity and create new knowledge on skin homeostasis.

participating in this dialogue, but also to comprehend how the interplay between these different components affects the innate immune system.

The project investigates how the communication between skin innate immunity and microbiota is mediated and will thereby provide us with deeper insight into the way in which the communication between microbiota and host regulates skin immunity and provide significant new knowledge on skin homeostasis and, possibly, novel therapeutic targets for treatment of inflammatory skin diseases. ✓

Funding and awards

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 13.2 million in 2020. SIC further acquired single-cell sequencing equipment at a value of DKK 4.2 million from a dedicated add-on grant. Also, the three basic research groups obtained a total of DKK 34.7 million in new funding from six external research grants. /

EXTERNAL RESEARCH GRANTS AWARDED IN 2020

FUNDER	RECIPIENT	AWARD TITLE	AMOUNT IN DKK
Independent Research Fund Denmark	Charlotte Menné Bonefeld	Characterisation of a novel type of rapid allergic reactions mediated by T cells	<u>2,560,263</u>
Independent Research Fund Denmark	Niels Ødum	Staphylococcus aureus as driver and therapeutic target in cutaneous T cell lymphoma	<u>5,983,200</u>
Innovation Fund Denmark	Anders Woetmann	Evaluation of key active components in non-steroid ointments for atopic dermatitis patients	<u>300,000</u>
Læge Sofus Carl Emil Friis og Hustru Olga Doris Friis' Legat	Charlotte Menné Bonefeld	Does house dust mite allergen immuno-therapy alter the allergen-specific immune response in the skin?	<u>500,000</u>
Novo Nordisk Foundation	Mads Gyrd-Hansen	Young Investigator Award	<u>25,000,000</u>
Translational Excellence Research Programme (Novo Nordisk Foundation)	Charlotte Menné Bonefeld	BRIDGE Fellowship	<u>1,130,000</u>

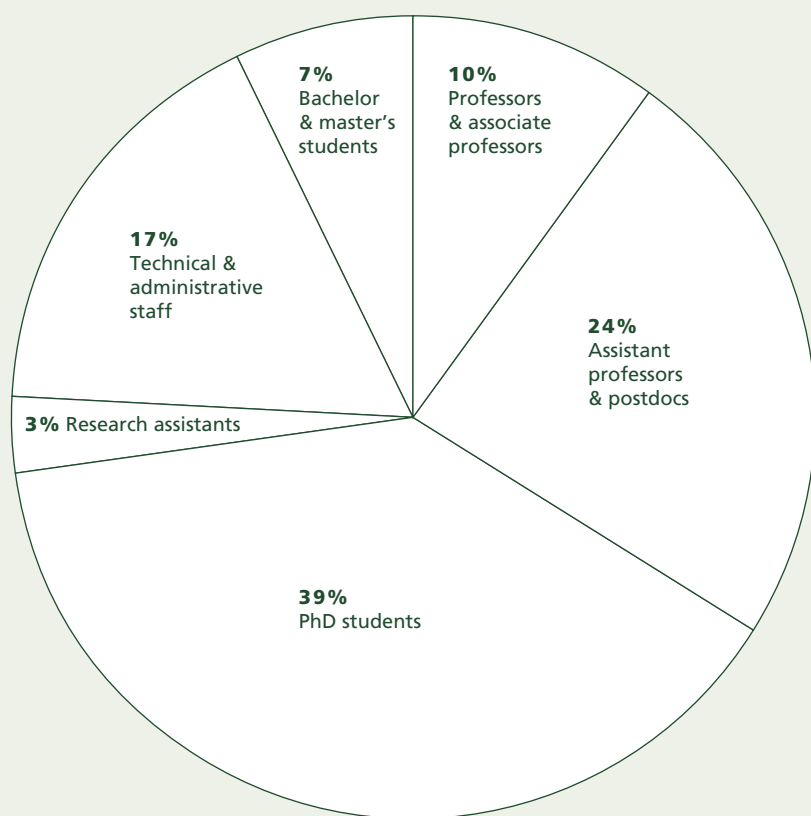
Organisation and governance

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 three basic research groups are based at the headquarters in the Mærsk Tower in the heart of Copenhagen. From here, scientific activities span widely, across the Faculty and across national and international clinical research units and the life science industry.

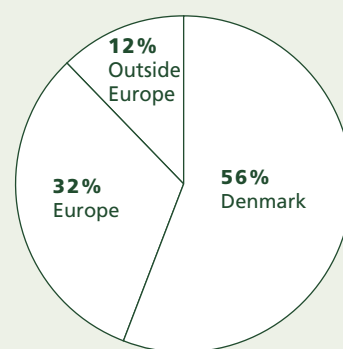
STAFF COMPOSITION

By the end of 2020, a total of 50 staff members and students of 12 different nationalities was engaged in SIC's three basic research groups. In 2020, SIC recruited nine new scientific staff members (recruitments and extensions), fully or partly financed by the SIC grant.

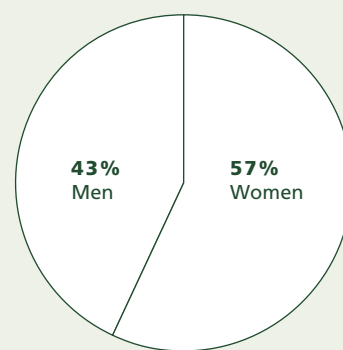
The compositional staff data presented here include visiting guest researchers, PhD students to whom SIC researchers provide main supervision and internal bachelor's and master's thesis students (students conducting their thesis work in SIC's laboratories). A full list of staff and students engaged in the research groups throughout the year is presented on page 35. /



Distribution of staff and students by position



Nationalities of scientific staff and students



Gender distribution

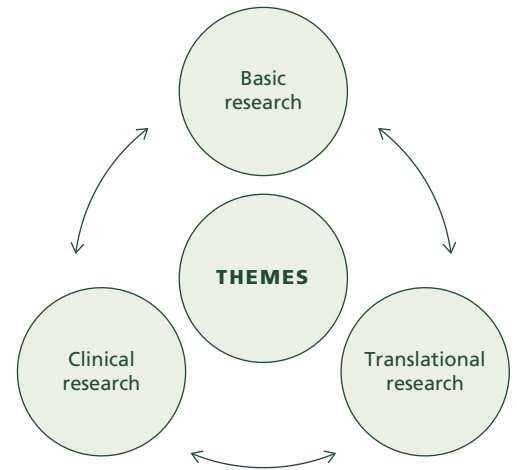
THE CORE MEMBERS

After the addition of one new basic research group in 2020, SIC now has four core members: Basic Research Group Leaders and Professors Charlotte Menné Bonefeld, Anders Woetmann and Mads Gyrd-Hansen and – as a representative of the translational and clinical research environment – Clinical Professor at Herlev and Gentofte Hospital, Jacob Pontoppidan Thyssen. The core members make up the Center Steering Committee which proposes and implements strategic scientific initiatives. The group of core members constitute the key framework behind the ‘Team Science Concept’.

MANAGEMENT

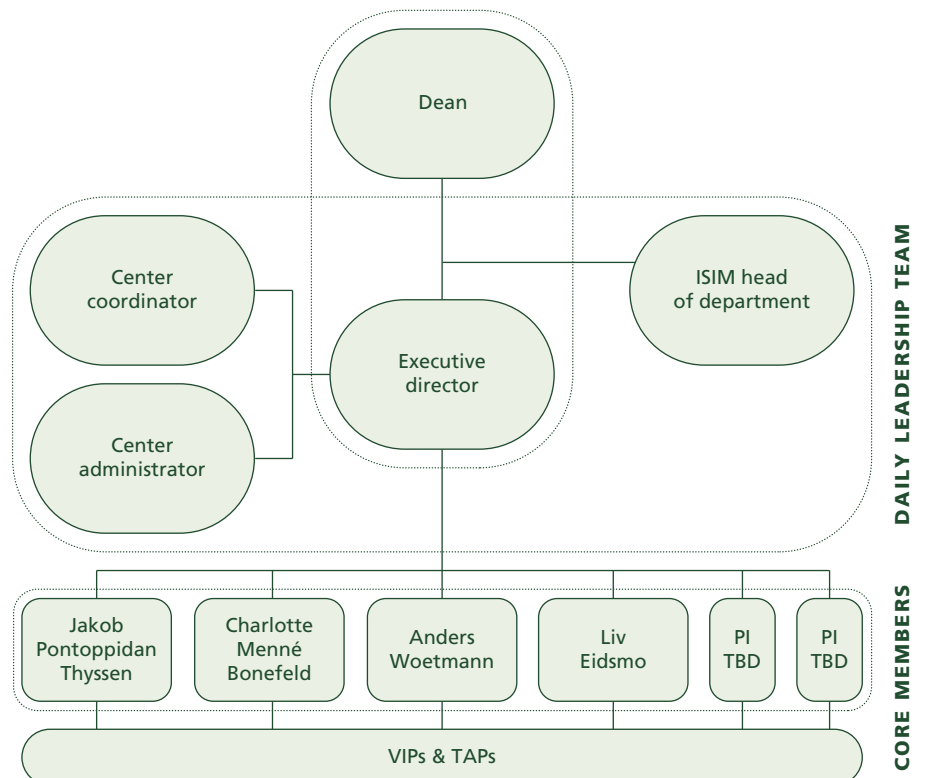
SIC’s Daily Leadership Team – consisting of Acting Executive Director Charlotte Menné Bonefeld, ISIM Head of Department Carsten Geisler, Center Administrator Nils Erik Samdal and Center Coordinator Bitten Dalsgaard – executes and oversees the Center’s day-to-day operations. The Executive Director and the leadership team meet with Dean of the Faculty, Ulla Wewer, on a regular basis to discuss and decide strategic matters related to the continuous development of SIC. Rector of the University of Copenhagen, Henrik C. Wegener, is the grant holder of the SIC grant and once a year aligns with the Center Management and the LEO Foundation on strategic progress and development.

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’.

STRATEGIC MANAGEMENT



Organisation and governance chart.

Outreach and communication

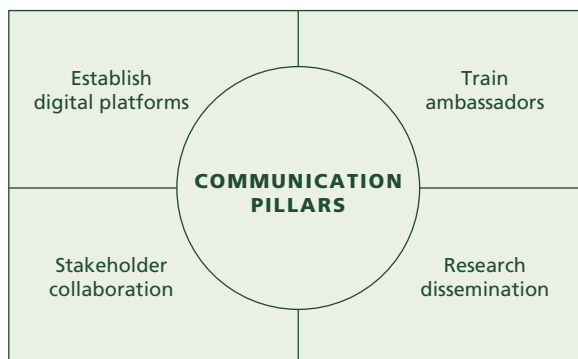
2020 has been a special year for SIC's planned communication activities and has opened up for new and alternative ways of presenting SIC as a visible public voice on skin, skin diseases and immunology.

The focus of the communication efforts completed in 2020 has been on 'explainer formats' with an aim of fulfilling multiple of the four pillars of communication simultaneously. The following examples show how to train scientist to disseminate their research to the public and stakeholders and how to make the strategic communication and outreach activities widely available on digital platforms.

An explanatory long read 'The Skin – the body's largest organ and defence system' was launched in May 2020. The goal was to present skin research in a simple and accessible manner from the perspective of the societal challenges within the area. The long read performed very well and enjoyed great exposure to both the general public and relevant stakeholders through the SIC, Faculty and University websites as well as the LEO Foundation's digital platforms.

A new video about skin disease research was produced in the summer of 2020 and also achieved great exposure through the University's websites and digital platforms. The video supports the Center's existing profile video, however, from a more explanatory angle and with in-depth information on methods and techniques applied in SIC's research projects. The video serves as a visual counterpart to the explanatory long read and as an appetiser for potential new researchers interested in joining the Center.

The sic.ku.dk website has undergone a significant upgrade in 2020 as the Center was selected as a first mover case to improve user experiences across University websites. The upgraded design uses many icons, facts and figures and visual contents as a way to present research and activities at centres and department.



Find us on social media

TWITTER @skinucph
LINKEDIN LEO Foundation Skin
Immunology Research Center

As for outreach, the planned activities were digitalised to the extent possible. The Danish nature and science festival Bloom launched a new digital universe, Bloom Explorer, where SIC was invited to do a talk. The talk was afterwards distributed to an international audience. SIC further launched a fall/winter seminar series that offered a variety of perspectives on skin and inflammation by covering areas ranging from stem cell biology to the clinical aspects. The series drew on expertise by some of the best researchers in SIC's immediate community. The seminar series continues in 2021 and is open to everyone.

In 2021, the focus in communication activities will be on training selected researchers as media ambassadors to strengthen dissemination through national and international media and social media. Communication activities will also have continued focus on recruitment of talented researchers and students. /



UPCOMING EVENTS

SIC's ongoing series of seminars and webinars by invited guest lecturers is open to everyone.

Visit sic.ku.dk/sic-calendar for details.

The 2021 EMBO workshop on 'Pathogen Immunity and Signalling' is co-organised by SIC Group Leader Mads Gyrd-Hansen and will be held on 26-30 September 2021 in France.

Visit embo.org/events for details.

The SIC Summer School on 'The Skin Barrier' will be held on 11-13 October 2021 in Hornbæk, Denmark.

Visit sic.ku.dk/summerschool for details.

SEMINARS AND WEBINARS BY INVITED GUEST LECTURERS

Resident T cells form localized disease memories in human skin

Associate Professor Liv Eidsmo
Department of Medicine, Solna,
Karolinska Institutet

Decoding the molecular anatomy of skin

Group Leader Maria Kasper
Department of Biosciences and Nutrition,
Karolinska Institutet

Atopic dermatitis in dogs – a shared disease complex between man and his best friend

Assistant Professor Mette Schjærff
Department of Veterinary Clinical Sciences,
University of Copenhagen

Immune cells at the skin stem cell niche: Sticking together through the good and the bad

Associate Professor Mirna Perez-Moreno
Department of Biology,
University of Copenhagen

From mechanistic insights to novel treatments for severe asthma – entering an era of targeted management

Professor Celeste Porsbjerg
Department of Respiratory Medicine,
Bispebjerg and Frederiksberg Hospital



SIC uses its unique headquarters on the 12th floor of the Mærsk Tower in the heart of Copenhagen as a platform for dissemination of skin and skin disease research and for engagement with the research community, stakeholders and the public. Photo: Adam Mørk for C.F. Møller.

Scientific output

SIC researchers authored 19 publications in peer-reviewed journals in 2020.
Bibliometric data of senior scientists and publications of the year are listed here.

Sources: Scopus, Web of Science

H-INDEX OF SENIOR SCIENTISTS

RESEARCHER	NO. OF PUBLICATIONS (TOTAL)	NO. OF CITATIONS (TOTAL)	H-INDEX
Professor Anders Woetmann	<u>115</u>	<u>4,037</u>	36
Professor Carsten Geisler	<u>186</u>	<u>5,893</u>	42
Professor Charlotte Menné Bonefeld	<u>106</u>	<u>2,395</u>	30
Professor Mads Gyrd-Hansen	<u>42</u>	<u>3,287</u>	25
Professor Niels Ødum	<u>290</u>	<u>9,417</u>	52
Associate Professor Thorbjørn Krejsgaard	<u>56</u>	<u>1,704</u>	25

PUBLICATIONS

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

Cellular Interactions and Inflammation in the Pathogenesis of Cutaneous T-Cell Lymphoma.

Stolearenco V, Namini MRJ, Hasselager SS, Gluud M, Buus TB, Willerslev-Olsen A, Ødum N, Krejsgaard T.

Front Cell Dev Biol. 2020 Sep 4;8:851. **5.186**

Dendritic Epidermal T Cells in Allergic Contact Dermatitis.

Mraz V, Geisler C, Bonefeld CM.

Front Immunol. 2020 May 19;11:874. **5.085**

Diagnostic Two-Gene Classifier in Early-Stage Mycosis Fungoides: A Retrospective Multicenter Study.

Nielsen PR, Eriksen JO, Lindahl LM, Wehkamp U, Bzorek M, Andersen G, Woetmann A, Iversen L, Ødum N, Litman T, Gjerdrum LMR.

J Invest Dermatol. 2020 May 23;S0022-202X(20)31599-2. **7.143**

Establishment of Prostate Tumor Growth and Metastasis Is Supported by Bone Marrow Cells and Is Mediated by PIP5K1 Lipid Kinase.

Karlsson R, Larsson P, Miftakhova R, Syed Khaja AS, Sarwar M, Semenas J, Chen S, Hedblom A, Wang T, Ekström-Holka K, Simoulis A, Kumar A, Ødum N, Grundström T, Persson JL.

Cancers (Basel). 2020 Sep 22;12(9):2719. **6.126**

Ex vivo culture of lesional psoriasis skin for pharmacological testing.

Tiirikainen ML, Woetmann A, Norsgaard H, Santamaria-Babí LF, Lovato P.

J Dermatol Sci. 2020 Feb;97(2):109-116. **3.681**

Filaggrin Expression and Processing Deficiencies Impair Corneocyte Surface Texture and Stiffness in Mice.

Thyssen JP, Jakasa I, Riethmüller C, Schön MP, Braun A, Haftek M, Fallon PG, Wróblewski J, Jakubowski H, Eckhart L, Declercq W, Koppes S, Engebretsen KA, Bonefeld C, Irvine AD, Keita-Alassane S, Simon M, Kawasaki H, Kubo A, Amagai M, Matsui T, Kezic S.

J Invest Dermatol. 2020 Mar;140(3):615-623.e5. **7.143**

Hypopigmented Mycosis Fungoides: Loss of Pigmentation Reflects Antitumor Immune Response in Young Patients.

Martínez Villarreal A, Gantchev J, Lagacé F, Barolet A, Sasseville D, Ødum N, Charli-Joseph YV, Hernández Salazar A, Litvinov IV.

Cancers (Basel). 2020 Jul 22;12(8):2007. **6.126**

Merkel cell carcinoma-derived exosome-shuttle miR-375 induces fibroblast polarization by inhibition of RBPJ and p53.

Fan K, Spassova I, Gravemeyer J, Ritter C, Horny K, Lange A, Gambichler T, Ødum N, Schrama D, Schadendorf D, Ugurel S, Becker JC.

Oncogene. 2020 Dec 11. **7.971**

MicroRNA-106b Regulates Expression of the Tumour Suppressors p21 and TXNIP and Promotes Tumour Cell Proliferation in Mycosis Fungoides.

Lindahl LM, Gluud M, Emmanuel T, Thomsen EA, Hu T, Rittig AH, Celis P, Stolearenco V, Krejsgaard T, Johansen C, Willerslev-Olsen A, Buus TB, Woetmann A, Aagaard L, Geisler C, Litman T, Mikkelsen JG, Odum N, Iversen L.

Acta Derm Venereol. 2020 Jun 18. **4.016**

MicroRNA-93 Targets p21 and Promotes Proliferation in Mycosis Fungoides T Cells.

Gluud M, Fredholm S, Blümel E, Willerslev-Olsen A, Buus TB, Nastasi C, Krejsgaard T, Bonefeld CM, Woetmann A, Iversen L, Litman T, Geisler C, Ødum N, Lindahl LM.

Dermatology. 2020 Apr 24;1-6. **3.695**

MicroRNAs in the Pathogenesis, Diagnosis, Prognosis and Targeted Treatment of Cutaneous T-Cell Lymphomas.

Gluud M, Willerslev-Olsen A, Gjerdrum LMR, Lindahl LM, Buus TB, Andersen MH, Bonefeld CM, Krejsgaard T, Litvinov IV, Iversen L, Becker JC, Persson JL, Korolov SB, Litman T, Geisler C, Woetmann A, Odum N.

Cancers (Basel). 2020 May 13;12(5):1229. **6.126**

Proinflammatory biomarkers are associated with prediabetes in patients with schizophrenia.

Marco Møller, Simon Fredholm, Mathias Ebbesen Jensen, Gitta Wörtwein, Julie Rask Larsen, Tina Vilsbøll, Niels Ødum, Anders Fink-Jensen.

CNS Spectr. 2020 Dec 14;1-8. **3.356**

Staphylococcus aureus alpha toxin inhibits CD8⁺ T cell-mediated killing of cancer cells in cutaneous T-cell lymphoma.

Blümel E, Munir Ahmad S, Nastasi C, Willerslev-Olsen A, Gluud M, Fredholm S, Hu T, Surewaard BGJ, Lindahl LM, Fogh H, Korolov SB, Rahbek Gjerdrum LM, Clark RA, Iversen L, Krejsgaard T, Bonefeld CM, Geisler C, Becker JC, Woetmann A, Andersen MH, Buus TB, Ødum N.

Oncoimmunology. 2020 Apr 17;9(1):1751561. **5.869**

Staphylococcus aureus enterotoxins induce FOXP3 in neoplastic T cells in Sézary syndrome.

Willerslev-Olsen A, Buus TB, Nastasi C, Blümel E, Gluud M, Bonefeld CM, Geisler C, Lindahl LM, Vermeer M, Wasik MA, Iversen L, Becker JC, Andersen MH, Gjerdrum LMR, Litvinov IV, Litman T, Krejsgaard T, Woetmann A, Ødum N.

Blood Cancer J. 2020 May 14;10(5):57. **8.023**

Suppressed microRNA-195-5p expression in mycosis fungoides promotes tumor cell proliferation.

Rittig AH, Johansen C, Celis P, Odum N, Litman T, Woetmann A, Lindahl LM, Iversen L.

Exp Dermatol. 2020 Jun 3. doi: 10.1111/exd.14124. **3.368**

The ectopic expression of meiCT genes promotes meiomitosis and may facilitate carcinogenesis.

Gantchev J, Martínez Villarreal A, Gunn S, Zetka M, Ødum N, Litvinov IV.

Cell Cycle. 2020 Apr;19(8):837-854. **3.699**

The metabolic enzyme arginase-2 is a potential target for novel immune modulatory vaccines.

Weis-Banke SE, Hübbe ML, Holmström MO, Jørgensen MA, Bendtsen SK, Martinenaite E, Carretta M, Svane IM, Ødum N, Pedersen AW, Met Ö, Madsen DH, Andersen MH.

Oncoimmunology. 2020 Jun 1;9(1):1771142. **5.869**

The Thioredoxin-Interacting Protein TXNIP is a Putative Tumour Suppressor in Cutaneous T-Cell Lymphoma.

Stolearenco V, Levring TB, Nielsen HM, Lindahl L, Fredholm S, Kongsbak-Wismann M, Willerslev-Olsen A, Buus TB, Nastasi C, Hu T, Gluud M, Côme CRM, Krejsgaard T, Iversen L, Bonefeld CM, Grønbaek K, Met Ö, Woetmann A, Ødum N, Geisler C.

Dermatology. 2020 Aug 14;1-8. **3.695**

T cells and inflammatory skin diseases.

Jee MH, Mraz V, Geisler C, Bonefeld CM.

Immunol Rev. 2020 Aug 27. **13.939**

Full staff list

PROFESSORS

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

ASSOCIATE PROFESSOR

- /// Thorbjørn Frej Krejsgaard

ASSISTANT PROFESSORS AND POSTDOCS

- / Andreas Willerslev-Olsen
- /// Anne-Sofie Østergaard Gadsbøll
- /// Berthe Katrine Fiil
- / Claudia Nastasi
- /// Emil Marek Heymans Pallesen
- /// John Rizk
- / Mandy Menzel
- / Martin Kongsbak-Wismann
- /// Mia Hamilton Jee
- /// Nicolai Skovbjerg Arildsen
- / Tea Kirkegaard Nielsen
- / Terkild Brink Buus

ASSOCIATED ASSISTANT PROFESSOR

- / Beatrice Dyring-Andersen

PHD STUDENTS

- / Anders Boutrup Funch
- / Anna Kathrine Obelitz Rode
- / Chella Krishna Vadivel
- / Cheng Chi
- / Daniel Villalba Lopez
- / Eileen Donohue Wedge
- / Fatima Abdul Hassan Al-Jaberi
- / Katharina Wörzner
- / Katrine Yderstræde Baumann
- // Kelvin Young
- / Laura Massarenti
- /// Lisa Harth
- / Lukas Peiffer
- / Maria Gluud Grøndahl
- / Maria Teresa Martin Monreal
- /// Marina Ramírez Galera
- /// Martin Rich Javadi Namini
- / Oliver Krigslund
- / Per Larsson
- /// Shayne Lavondua Ford
- /// Veronika Mraz

RESEARCH ASSISTANTS

- /// Frederik Timmermann
- /// Veronica Stolareenco

GUEST RESEARCHERS

- // Marina Passos Torrealba
- / Sara Torres Rusillo

INTERNAL MASTER'S THESIS STUDENTS

- / Siri Svarre Hasselager
- / Søren Vester Kofoed
- / Tinghaun Song

INTERNAL BACHELOR THESIS STUDENT

- / Ida Sandau Sørensen

LAB MANAGERS, TECHNICIANS AND ASSISTANTS

- / Cecilie Hald Andersen
- / Julie Weber Friis
- / Louise Mørk
- / Nadja Thisted Sauerberg
- / Sana Ahmed

SPECIALIST OPERATOR

- /// Rasmus Nielsen Klitgaard


STUDENT ASSISTANTS

- / Emilia Sæderup Lindeløv
- / Gustav Ørting Jørgensen

ADMINISTRATION

- /// Bitten Dalsgaard
- // Mette Malene Odgaard
- // Nils Erik Samdal

- /// Funded by the SIC grant
- // Partly funded by the SIC grant
- / Not funded by the SIC grant

The background of the entire page is a dark green color. Overlaid on this is a pattern of numerous small, light green, hand-drawn style outlines of skin cells. These cells are irregular in shape, mostly oval or rounded, and each contains a small circle representing a nucleus. The pattern is dense and covers the entire page, with a slight gradient in density, being more concentrated on the left side and fading towards the right.

LEO Foundation
Skin Immunology
Research Center

ADDRESS Blegdamsvej 3b
2200 Copenhagen N
Denmark

EMAIL sic@sund.ku.dk

PHONE +45 20 40 22 68

WEB sic.ku.dk

TWITTER @skinucph