EDITORIAL

Dear colleagues and friends,

A few weeks ago, an era has come to an end. Prof. Gerold Schuler, founding member of the Medical Immunology Campus and director of the Department of Dermatology for almost 24 years, has officially retired. The Medical Faculty, the University Hospital and the immunology community in Erlangen owe Gerold Schuler a lot. Gerold has been a driving force in expanding translational and clinical immunology at our campus. He initiated and led the Collaborative Research Center (CRC) 643 on cellular strategies of immune intervention for the maximum funding period of 12 years from 2004 to 2012. This was the first CRC that included clinical trial projects. With the foundation of the GMP facility on the Hartmann Straße Campus, he set the infrastructural stage for implementing dendritic cell-based immunotherapy into the treatment of patients with malignancies such as melanoma. In his department, he succeeded to spread a “dendritic cell spirit” that led to an impressive dedication and perseverance amongst his coworkers. Everybody who attended his farewell lecture on October 11 and the minisymposium on cancer vaccines and dendritic cells on October 12 (see separate report in this newsletter), could witness his contagious and undiminished enthusiasm for basic and clinical science and, of course, for these “magic DCs”. On behalf of the entire campus, I wish to cordially thank you, Gerold, for your kindness, support and vision that very much contributed to the leading position of immunological research at FAU!

On November 19, Prof. Dolores Schendel, Chief Scientific and Executive Officer of Medigene company, visited Erlangen to deliver the 11th Joachim Kalden Lecture. Dolores gave fascinating insights into the tumor immunotherapeutic approaches that are developed at Medigene (see separate report in this newsletter).

Approaching the end of the year 2019, it is fair to state that the Medical Immunology Campus Erlangen continues to thrive. In the new elite M.Sc. course “Integrated Immunology” the first cohort of students has passed the basic, translational and clinical immunology training and is now on its way to the international lab rotations. Three new initiatives for collaborative research consortia (run by Aline Bozec, Rainer Böckmann and Falk Nimmerjahn, and by Thomas Brabletz) have been started. The on-site review of the Research Training Group “FAIR – Feinabstimmung der adaptiven Immunität” (designated spokesperson: Hans-Martin Jäck) will take place in January 2020. With the help of a FAU Connect grant, a retreat is planned in April 2020 to pursue the research concept of “Immunophysics”. In this context, we also hope that the construction of the building for the Max Planck Center for Physics and Medicine commences in the year 2020.

I wish you and your families a Merry Christmas, happy holidays and all the best for the start of the new decade.

Prof. Christian Bogdan
Chairman of The Medical Immunology Campus Erlangen
Visualization and deletion of alternatively activated macrophages in vivo

*RELM*α-expressing macrophages protect against fatal lung damage and reduce parasite burden during helminth infection

DAVID VÖHRINGER
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Newly generated RELMα fate mapping mice reveal a critical role for alternatively activated macrophages in protection against helminths and restoration of tissue integrity.

Alternatively activated macrophages (AAMs) increase during type 2 immune responses elicited by helminth infection and allergic inflammation. They express a variety of IL-4- or IL-13-induced effector molecules associated with tissue remodeling and wound healing, including arginase 1, chitinase-like proteins and resistin-like molecule alpha (RELMα). The *in vivo* functions of AAMs are incompletely understood.

We recently generated fate mapping mice, in which cells that express RELMα are stably marked by a fluorescent protein. Using this system, we found that RELMα+ macrophages increase in the interstitium of the lung after infection with the helminthic parasite *Nippostrongylus brasiliensis* (*Nb*) in a STAT6-dependent manner.

To further reveal their function during helminth infection, we crossed the mice to CD115_iDTR mice so that RELMα+ macrophages were deleted by administration of diphtheria toxin. Deletion during primary *Nb* infection resulted in fatal lung damage due to impaired restoration of tissue integrity. A secondary *Nb* infection usually results in efficient larval trapping in the skin. This protective immune response was lost when RELMα+ macrophages were depleted.

Our results demonstrate that AAMs play a critical, non-redundant role for protective immunity against helminths and for repair of damaged tissue.


Macrophages are considered to act as central cells of host defense, but have also been implicated in the pathogenesis of chronic inflammatory diseases. By applying multiple fate-mapping approaches in conjunction with 3D-light-sheet fluorescence microscopy and single cell RNA sequencing, we performed a comprehensive spatiotemporal analysis of the composition, origin and differentiation of monocyte and macrophage subsets within the healthy and inflamed joint to study their individual roles during inflammatory joint diseases such as rheumatoid arthritis (RA). This approach revealed highly dynamic membrane-like structures consisting of a distinct population of tissue-resident CX3CR1+ TREM2+ synovial macrophages that formed an internal immunological barrier and physically secluded the entire joint in mice and humans.

Importantly, these barrier-forming macrophages displayed functional features otherwise typical of epithelial cells, and displayed an immune-modulatory phenotype as well as tight junctions. They constantly maintained their numbers through a pool of locally proliferating CX3CR1– mononuclear cells embedded into the synovial tissue and thus existed independently of blood monocytes. During joint inflammation, the identified epithelial-like CX3CR1+ TREM2+ synovial lining macrophages restricted the inflammatory reaction by providing a tight junction-mediated shield for intra-articular structures, whereas newly recruited monocyte-derived macrophages actively contributed to joint inflammation. During chronic inflammatory joint diseases such as RA, in turn, the macrophage barrier disappears, which likely contributes to the chronification of disease. Our data show an unexpected functional diversification among tissue-resident synovial MΦs and identify distinct tissue-resident macrophages that repopulate, differentiate and self-organize in an epithelium-like manner, physically sealing the joints and protecting them from inflammation-associated tissue-damage.

Bioinformatics-based prediction and selection of efficacious and tolerable tumor epitopes for therapy

Curatopes Melanoma is a database and a decision support system for the selection of computationally predicted T-cell epitopes from proteins overexpressed in metastatic melanoma

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Therapeutic vaccination against solid tumors is an immunotherapy with a long history of clinical investigation. Despite being recently sidelined by the success of checkpoint inhibitors, it remains an active area of research due to its assumed specificity, tolerability, and its conceptual ties to the idea of cancer prophylaxis.

One of the key steps in anti-cancer vaccination is the selection of one or more suitable antigens. Apart from efficacy, the avoidance of life-threatening autoimmune reactions and a resource-efficient clinical use are of particular importance. With these points in mind, we set out to define cohort-specific, non-mutated peptide antigens that can be mass-produced and stored as libraries for later use.

Our idea was to combine next-generation sequencing data from metastatic melanoma samples, bioinformatics algorithms and data from frequencies of HLA alleles. We systematically compared the expression landscape of metastatic cutaneous melanoma biopsies with that of control tissues from characterized organs. Selecting physiologically undetectable proteins with increased mRNA expression in melanoma biopsies, we predicted epitopes from their cognate peptides of length 9 to 12 and from compatible MHC-I alleles. Epitopes, whose peptides lacked sequence duplicates in other proteins, were scored according to their predicted efficacy and made publicly available at www.curatopes.com.

After experimental validation, the peptides presented in Curatopes could be used as principal or adjuvant treatment in clinical trials on metastatic melanoma, with dendritic cells, CAR T-cells, or other delivery systems as vectors. We are currently extending the database to additional highly metastatic tumors.

CD4+ T cells play a central role in orchestrating innate and adaptive immunity. This requires processing and presentation of class II-restricted antigens on antigen-presenting cells (APC). However, during the formation of cancer, many degenerated cells develop strategies to evade direct recognition by the host, such as the downregulation of MHC molecules. In spite of this escape strategy, recent studies have demonstrated that CD4+ T cells can efficiently reject MHC class II-negative tumors. Yet, it is doubtful whether the antigen-transfer to surrounding and class II-positive APC can be attributed solely to uncontrolled antigen release by cell death.

We hypothesized that intercellular transfer of proteins depends on heat-shock cognate protein 70 (HSC70) and its KFERQ-like binding motif on substrate proteins. Using human Y chromosome antigen DBY, we showed that mutation of one of its two putative KFERQ-like binding motifs significantly diminished T cell activation after indirect presentation and reduced protein-protein interaction with HSC70. Our work further demonstrated that intercellular antigen-transfer was independent of cell-cell contact, but relied on engulfment within secreted microvesicles, reflecting a host cell controlled mechanism to sequester molecules. In vivo, alterations of the homologous KFERQ-like motif in murine DBY hampered tumor rejection, T cell activation, and migration into the tumor and significantly impaired survival.

Collectively, we showed that intercellular antigen transfer of DBY is tightly regulated via binding to HSC70 and that this mechanism influences recognition and rejection of class II–negative tumors in vivo.
Blood vessels offer new approaches for treating chronic inflammatory bowel diseases

Interferon-γ drives inflammatory bowel disease pathogenesis through vascular-endothelial-cadherin-directed vascular barrier disruption

VICTORIA LANGER, NATHALIE BRITZEN-LAURENT, MICHAEL STÜRZL

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In Germany alone, there are around 400,000 patients who suffer from chronic inflammatory bowel diseases. While it is well known that inflammatory cells can only reach the relevant tissue via blood vessels, the role of blood vessels in chronic inflammatory bowel diseases has not yet been thoroughly investigated.

We discovered that the blood vessels of patients with chronic inflammatory bowel disease are particularly permeable. In molecular analyses, we identified a malfunction in the cell-to-cell interaction of endothelial cells as the underlying mechanism. Endothelial cells form the lining of blood vessels and are responsible for maintaining vessel wall impermeability. The dysfunction is caused by a specific cytokine known as interferon-γ, which is present in higher concentrations in chronically inflamed intestinal tissue. The increased permeability of blood vessels was proven in various experimental models and, most importantly, in patients with chronic inflammatory bowel diseases.

The significance of blood vessel permeability was demonstrated in experiments using genetic animal models, where the ability of endothelial cells to react to interferon-γ was inhibited, which significantly slowed down the progression of the disease. A significant clinical finding was that the drug imatinib (Glivec®) inhibited vessel permeability, which also significantly suppressed disease progression. Imatinib (Glivec®) is currently mainly used to treat cancer.

Our study proves for the first time the great significance of the vascular system in chronic inflammatory bowel diseases and opens up new approaches for treatment.

Human cytomegalovirus (HCMV) is a betaherpesvirus with a large DNA genome that persistently infects a high percentage of the human population. Although usually asymptomatic, CMV infection is the most frequent cause of birth defects due to congenital viral infections and a major health risk for immunocompromised individuals, such as transplant recipients or HIV-positive patients.

SAMHD1 is a dNTP triphosphohydrolase that inhibits retroviruses in non-dividing myeloid cells by depleting the intracellular dNTP pool. Although CMV also targets myeloid cells, the role of SAMHD1 during CMV infection remained elusive. Thus, we used murine CMV to infect previously established SAMHD1 knockout (KO) mice and found that SAMHD1 suppressed MCMV replication in vivo. By infecting myeloid cells from KO and control mice, we identified the viral kinase M97 to counteract SAMHD1. M97 phosphorylates SAMHD1 at the regulatory residue threonine 603 correlating with a reduced dNTP hydrolase activity, enhanced CMV genome replication, and the loss of viral restriction.

Together with Prof. Michael Schindler from the University of Tübingen, we were able to confirm these findings for HCMV. We found that SAMHD1 blocked HCMV infection of primary human macrophages and that HCMV overcame this block by counteracting SAMHD1 through phosphorylation via UL97, the HCMV homologue of M97.

Together, we have shown for the first time that the betaherpesvirus CMV is targeted by the innate immune factor SAMHD1 in primary cells in vitro and that SAMHD1 restricts MCMV replication in vivo. In addition, we have identified the viral kinases M97 and UL97 as novel means to counteract the restriction factor SAMHD1 in non-dividing cells by phosphorylation.


**SCIENTIFIC HIGHLIGHTS**

**Fueling Replication – how CMV gets its DNA building blocks**

A viral kinase counteracts in vivo restriction of murine cytomegalovirus by SAMHD1

**THOMAS GRAMBERG**

INSTITUTE FOR CLINICAL AND MOLECULAR VIROLOGY, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

Model of the interaction between host factor SAMHD1 and the viral kinase M97. As important component of dNTP metabolism, active SAMHD1 is responsible for low intracellular dNTP concentration. Our data indicate that upon MCMV infection, SAMHD1 is inactivated through phosphorylation by the viral kinase M97, leading to increased dNTP levels and consequently to elevated viral genome replication and production of infectious virus.
October 2019 saw the celebration of Professor Schuler’s well-deserved retirement from his scientific activities. On October 11, Gerold Schuler, who has been the director of the Department of Dermatology at the Universitätsklinikum Erlangen for nearly 24 years, gave his FAU farewell lecture, in which he reviewed the development of the tumor immunotherapy and highlighted some of the achievements of his department.

On October 12, many internationally renowned cancer immunologists as well as various members of the Medical Immunology Campus Erlangen paid their respect to Prof. Schuler in the form of participating as guest speakers and discussants in a minisymposium on Cancer Vaccines and Dendritic Cells, which took place in the Novotel Erlangen. The day was filled not only with presentations of cutting-edge research data but also offered plenty of opportunities for scientific and non-scientific discussions.

Gerold Schuler was born in 1951 in Innsbruck, Tyrol, Austria and completed his medical studies at the Leopold Franzens University in Innsbruck, graduating with distinction in 1975. In 1983, shortly after being recognized by the Austrian Medical Association as specialist for dermal and venereal diseases, Gerold Schuler spent three years at Rockefeller University in New York in the laboratory of Prof. Dr. Ralph Steinman, the discoverer of “dendritic cells”, where he developed the concept of the maturation of dendritic cells that turned out to be an essential control point in the immune system. After returning to the University of Innsbruck in 1985, his work focused on the use of dendritic cells for human vaccination. Together with his group, he designed a protocol for the reproducible cultivation of human dendritic cells from monocytes using the combination of GM-CSF and IL-4. On November 1, 1995, Gerold Schuler became director of the Department of Dermatology at the Universitätsklinikum Erlangen, where he spent many years improving his method, establishing a GMP laboratory and carrying out several very successful phase I and II studies. These studies proved that dendritic cell vaccines not only induced a strong immune response in melanoma patients but also led to a prolonged survival or even cure in some of the vaccinated patients.

Prof. Schuler’s work has received national and international recognition in many ways. He has been an adjunct member of Rockefeller University since 1992, a member of the Austrian Academy of Sciences, a spokesperson for the Collaborative Research Centre SFB643 “Strategies of Cellular Immune Intervention”, a member of the DFG Senate, and the coordinator for the therapeutic application of dendritic cells in EU projects such as the DC THERA Network of Excellence or the CIMT Integrated Project. Furthermore, Gerold Schuler received numerous awards such as the German Cancer Award in 2006 and the Unna Medal in 2019.

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The Medical Immunology Campus Erlangen gratefully acknowledges the achievements of Prof. Schuler and wishes him all the best for the years to come after his retirement. Ad multos annos!
## PEOPLE

### Dr. med. Andreas Ramming

Andreas Ramming received the highly coveted and competitive ERC starting grant

Dr. Ramming, physician and research group leader at the Department of Medicine 3, Universitätsklinikum Erlangen, succeeded in obtaining the renowned ERC starting grant worth 1.5 Mio Euro (rate of grant approval less than 10%). With this ample funding, the European Research Council (ERC) supports up-and-coming research leaders across Europe for the duration of five years. Andreas Ramming intends to develop a completely new therapeutic approach for autoimmune diseases such as psoriasis that prevents the spread of inflammation right from the start instead of treating it symptomatically afterwards.

### Prof. Dr. rer. nat. Aline Bozec

Appointment as W2 Professor for Experimental Immunology and Immunotherapy at the Department of Medicine 3 – Rheumatology and Immunology of the Universitätsklinikum Erlangen

Aline Bozec, born in France, obtained her PhD degree in Biochemistry in 2004 from the University Claude Bernard Lyon, where she worked on the effects of in utero exposure to environmental factors as endocrine disruptors on male fertility.

In 2005, she joined Prof. Erwin Wagner’s Laboratory at the Research Institute of Molecular Pathology (IMP) in Vienna, Austria. In Vienna, her research focused on the fundamental aspects of AP-1 transcription factors on bone biology. In 2008, she moved to the Spanish National Cancer Research Centre-CNIO in Madrid, Spain, as a Staff scientist under Erwin Wagner’s supervision.

In January 2012, she joined the Department for Medicine 3 – Rheumatology und Immunology in Erlangen as junior professor in osteoimmunology and head of an Emmy Noether independent junior research group focusing particularly on cross-talk between metabolism bone homeostasis and inflammation.

We congratulate Aline Bozec on her appointment as W2 Professor for Experimental Immunology and Immunotherapy and wish her good luck and success for her future.
PEOPLE

Prof. Dr. rer. nat. Mario Zaiss
Appointment as W2 Professor for Immune Tolerance and Autoimmunity at the Department of Medicine 3 – Rheumatology and Immunology of the Universitätsklinikum Erlangen

Mario Zaiss studied Biology at the Universities of Bremen and Heidelberg and obtained his doctoral degree at the FAU Erlangen-Nürnberg at the Department of Medicine 3, Universitätsklinikum Erlangen, in 2009. After his postdoctoral studies at the École polytechnique fédérale de Lausanne (EPFL), Switzerland, he spent one year in industry working as a project manager and entrepreneur in a start-up company. Prof. Zaiss returned to the Universitätsklinikum Erlangen in 2016 and started working on the role of microbial metabolites in the pathogenesis of chronic inflammatory diseases.

We congratulate Mario Zaiss on his appointment as W2 Professor for Immune Tolerance and Autoimmunity and wish him best of luck for his future research.

NEWS AND UPDATES

Joachim Kalden Lecture 2019
The Medical Immunology Campus Erlangen honors Prof. Dr. Dolores J. Schendel

The Joachim Kalden Lecture 2019, which took place on November 19, 2019, was delivered by Professor Dolores Schendel, Chief Executive and Chief Scientific Officer at Medigene AG, Planegg/Martinsried.

Dolores Schendel’s main research interests focus on T-cell-based immunotherapies against cancer that are individually tailored to the patient. Prof. Schendel earned her PhD degree in genetics at the University of Wisconsin, USA, followed by post-doctoral training in immunology at University College London, UK. She developed her interest in tumor immunology while working at the Sloan-Kettering Institute for Cancer Research in New York. She soon led her own junior research group and, in 1986, became professor of immunology at the Institute of Immunology, Ludwig-Maximilian-University (LMU), Munich. From 1999 to 2013, she was director of the Institute of Molecular Immunology of the German Research Center for Environmental Health at the Helmholtz Center Munich. In 2013, Prof. Schendel founded and became managing director of Trianta Immunotherapies GmbH, which in 2014 was taken over by Medigene AG in Martinsried, Germany. Prof. Schendel currently serves as Chief Scientific and Chief Executive Officer at Medigene.

Dolores Schendel is the author of more than 200 scientific publications, has spent several decades as a scientific review board member in various research organizations such as the German Research Foundation, German Cancer Aid and the European Research Council among others. She is a recipient of the German Federal Order of Merit and the Bavarian Order of Merit and received the ‘Deutsche Krebshilfe Preis’, the award of the German Cancer Aid. In the 1990s, Prof. Schendel was repeatedly member of the reviewing panel that evaluated the CRC 263 “Autoimmunity, Inflammation and Infection”, which was run by Prof. Joachim Kalden as spokesperson.

Prof. Schendel delivered a captivating lecture entitled “My Journey to Join the Frontline in TCR-T Immunotherapies”. She presented new and exciting data on Medigene’s technology for T cell receptor-modified T cells that is particularly suited for the treatment of advanced cancer. The aim is to arm the patient’s own T cells with tumor-specific T cell receptors that are isolated from hundreds of T cell clones (derived from young healthy donors and reacting with dendritic cells laden with tumor antigens) and are available “off the shelf” in form of retroviral vectors. The receptor-modified T cells
are then able to detect and efficiently kill tumor cells. This form of immunotherapy aims to overcome the patient’s tolerance to cancer cells, and the tumor-induced immunosuppression in the patient, by activating and modifying the patient’s T cells outside the body (ex vivo). Another promising immunotherapeutic strategy is the design of costimulatory switch receptors. Here, T cells express a PD1/4-1BB hybrid molecule so that they become activated rather than suppressed after contact with PD-L1-expressing tumor cells.

UPCOMING EVENTS

Immunological Colloquium of the Medical Immunology Campus Erlangen – Winter 2019/20

Tuesdays, 5.15 pm

07.01.2020
Dr. Silvia Portugal
Department of Infectious Diseases, Parasitology, Heidelberg University Hospital
Plasmodium falciparum dry season reservoir: a long hide and seek game

14.01.2020
PD Dr. Marta Rizzi
Klinik für Rheumatologie und Klinische Immunologie, Universitätsklinikum Freiburg
To B or not to B: developmental decisions in human B cells

21.01.2020
Prof. Christopher Linington
Institute of Infection, Immunity & Inflammation, University of Glasgow, UK
Antibody-mediated activation of microglia: a generalised treatment strategy for viral encephalitis

28.01.2020
Dr. Elodie Segura
INSERM, Institut Curie, Centre d’Immunothérapie, Paris, France
to be announced

04.02.2020
Dr. Christoph Klose
Charité - Universitätsmedizin Berlin
Immune regulation at barrier surfaces by group 2 innate lymphoid cells

03.03.2020
Dr. Sebastian Winter
Department of Microbiology, UT Southwestern Medical Center, Dallas, TX, USA
Microbiota Metabolism and Intestinal Inflammation
UPCOMING EVENTS

Conferences and Events of Interest

March 4 – 6, 2020 • Burg Rothenfels
Meeting des AK Infektionsimmunologie

March 8 – 11, 2020 • Leipzig
72. DGHM-Jahrestagung 2020
6. Gemeinsame Tagung von DGHM und VAAM
www.dghm-kongress.de

March 12 – 14, 2020 • Sonthofen, Bayern
Meeting des AK Biologie der B-Lymphozyten

March 18 – 19, 2020 • Resort Schwielowsee, Potsdam
Meeting des AK Klinische Immunologie

March 25 – 28, 2020 • Berlin
30th Annual Meeting of the Society for Virology
www.virology-meeting.de

April 18 – 21, 2020 • Paris, France
30th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
www.eccmid.org/eccmid_2020

May 14 – 16, 2020 • Halle/Saale
Meeting des AK Tumorimmunologie

May 20 – 24, 2020 • Athens, Greece
12th International Congress on Autoimmunity
www.autoimmunity.kenes.com

May 27 – 30, 2020 • Mallorca, Spain
2nd International Congress of Micro-Immunotherapy
www.icomi2020.org

June 18 – 20, 2020 • Aarhus, Denmark
34th Conference of the European Macrophage and Dendritic Cells Society
https://conferences.au.dk/emds/

July 2 – 3, 2020 • Marburg
Meeting des AK T-Zellen

October 11 – 15, 2020 • Queensland, Australia
16th International Symposium on Dendritic Cells 2020
www.dc2020symposium.com