Dear colleagues and friends,

Since the publication of the last newsletter the Medical Immunology Campus Erlangen has received a number of positive decisions from the German Research Foundation (DFG): at the end of November the Transregio Collaborative Research Center TRR221, which focuses on the modulation of graft-versus-host and graft-versus-leukemia immune reactions after allogenic stem cell transplantation, was approved. The TRR221 (spokesman: Wolfgang Herr, Regensburg; co-spokesman: Andreas Mackensen, Erlangen) is a joint venture of the universities of Regensburg, Erlangen and Würzburg and is certainly an excellent opportunity to strengthen the ties between the northern Bavarian universities. In May 2018, the application for a collaborative research center on immune-epithelial communication in inflammatory bowel diseases (TRR241) also successfully passed the senate committee of the DFG. The TRR241 (spokesperson: Christoph Becker, Erlangen; co-spokesperson: Britta Siegmund, Berlin) is a collaborative effort of FAU investigators and researchers from the Charité University Medicine and German Rheumatology Research Center in Berlin. These two TRRs will undoubtedly further broaden the spectrum and increase the visibility of immunological research at FAU. On behalf of all members of our campus I particularly thank Andreas and Christoph for their commitment and congratulate them for these achievements. The third piece of good news from the DFG also arrived in May and concerned the application of Klaus Überla for a research training group on novel antiviral approaches, which was invited for a full proposal.

During the recent professors’ convention of the Medical Faculty, Georg Schett highlighted not only the current immunological consortia, but also presented a series of new research initiatives in the field of immunology and infectious diseases. These are (a) the Research Unit on “Pathways triggering autoimmunity and defining onset of early rheumatoid arthritis” (FOR2886 “PANDORA”; designated spokespersons are Gerhard Krönke and Mario Zaiss), which will be evaluated on-site in September; (b) the Research Training Group on microenvironmental, metabolic and microbial signals regulating immune cell-pathogen interactions (GRK 2259 “ImmunoMicroTope”, designated spokesperson Christian Bogdan), the proposal of which was submitted in April; (c) the Research Unit “Immune and Neuronal Crosstalk” (designated spokesperson: Alexander Steinkasserer; preproposal will be submitted shortly); and (d) the Research Training Group on molecular stimuli and controllers of adaptive immunity (designated spokesperson: Hans-Martin Jäck; preproposal in preparation). All these initiatives are reflecting the steadily increasing number of independent immunological research groups at our campus.

Finally, I would like to inform you that on July 13 there will be the inauguration of the “Deutsches Zentrum für Immuntherapie” at our university and university hospital in the presence of Professor Harald zur Hausen, who formerly headed the Institute of Virology at FAU and the German Cancer Research Center in Heidelberg and received the Nobel Prize in Medicine in 2008 for his discovery of human papilloma viruses causing cervical cancer. He will also deliver the key address during the graduation ceremony at the Faculty of Medicine on July 14. Please try to attend these two exciting events.
SCIENTIFIC HIGHLIGHTS

**Novel T cell subset promotes intestinal GvHD**

*IL-7Rhi GM-CSF+ T cells control intestinal Graft-versus-Host disease formation in a BATF-dependent, but Th17 cell-independent manner*

BENJAMIN ABENDROTH, KAI HILDNER
DEPARTMENT OF INTERNAL MEDICINE 1, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

Acute Graft-versus-Host disease (GvHD) represents a severe, T cell–driven inflammatory complication following allogeneic hematopoietic cell transplantation. GvHD often affects the intestine and is associated with a poor prognosis. Detailed knowledge on the cues driving donor T cell differentiation into GvHD-mediating effector cells is still limited. Although Th17 cells have been repeatedly implicated, direct and functional proof of their relevance is lacking.

Importantly, we found that T cells lacking Th17 cell potential due to the genetic inactivation of the transcription factor BATF fail to induce intestinal GvHD. Initially attributing this result to hampered Th17 differentiation, we surprisingly found that the colonic pool of Batf−/− T cells was largely depleted of GM-CSF+ T cells. Interestingly, besides BATF-dependent differentiation of IL-7-induced GM-CSF+ T (Thgm) cells *in vitro*, complementation of previously Batf−/− donor T cell receiving mice with IL-7Rhi colonic T cells isolated from intestinal GvHD-affected mice and enriched for GM-CSF producers reconstituted colitis *in vivo* suggesting that indeed GM-CSF-expressing T cells play a functionally pivotal role in this context. Finally, the combined antibody-mediated blockade of IL-7/IL-7R interaction and GM-CSF protein in mice receiving BATF- and hence Th17-competent donor T cells largely protected against intestinal GvHD formation overall indicating that IL-7Rhi GM-CSF+ T cells are critical mediators of allo-response driven colitis in a Th17-independent manner.

Together, BATF-dependent, IL-7 responsive ThGM-CSF cells are critical promoters of intestinal GvHD. Future studies need to further evaluate whether targeting ThGM-CSF cells represents a novel promising option to restrain intestinal GvHD in patients.


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**Model**

During development, ThGM-CSF and Th17 cells are comparably dependent on T cell-intrinsic BATF, whereas both subsets display distinguishable dependencies on “signal 3” - i.e. IL-23 vs. IL-7 - during differentiation and contribute to the course of syngeneic (e.g. inflammatory bowel disease, IBD) vs. allo-response-driven (i.e. intestinal GvHD) colitis in a subset-specific manner.
Checking the immunometabolic balance
The PD-1/PD-L1 axis impacts the immunometabolic fitness of monocytes in CLL

DIMITRIOS MOUGIAKAKOS
DEPARTMENT OF INTERNAL MEDICINE 5, HEMATOLOGY AND ONCOLOGY,
FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIUM ERLangen

Chronic lymphocytic leukemia (CLL) is the most common leukemia amongst adults in the Western world. The use of monoclonal antibodies against CD20 has proven efficient in CLL treatment. Emerging evidence suggests that the metabolic repertoire and adaptability of immune cells strongly determines their function. Monocytes and macrophages represent key components for intrinsic (innate) anti-tumor immunity and as mediators of phenomena elicited by the therapeutic antibodies such as antibody-dependent phagocytosis and antibody-dependent cytotoxicity. Despite the monocytes’ prominent role little is known regarding their immunometabolic status in cancer and specifically in CLL.

Here, we set out to explore (A) metabolic changes in CLL-derived monocytes, (B) links between their energy metabolism and anti-tumor activity, and (C) potential targetable underlying mechanisms. Parameters indicative for glucose metabolism were found at lower levels in CLL-monocytes as compared to their healthy donor-derived counterparts. CLL-monocytes failed to undergo a glycolytic shift during differentiation into type 1 macrophages. Furthermore, we were able to show that fine tuning glycolytic activity controlled the ability of monocytes to ingest CLL-cells opsonized using anti-CD20 antibodies: promotion of glycolysis (by e.g. insulin) enhanced while inhibition of glycolysis (by e.g. 2-deoxy-glucose) limited phagocytosis.

In addition, we observed an increased expression of the immunological checkpoint PD-1 on CLL-cells and of its cognate receptor PD-L1 on CLL-monocytes. In fact, triggering the PD-1/PD-L1 axis reduced glycolytic together with phagocytic activity in monocytes. As anticipated, interfering with PD-1/PD-L1 crosstalk restored immunometabolic competence, which could partly explain the clinical success of immune checkpoint inhibitors and should be further therapeutically exploited.

Immunometabolic modulation by PD-1. (1.) Circulating CLL-cells display increased levels of the immune checkpoint (ICP) PD-1 on their cell surface. Their cognate receptor PD-L1 is abundantly expressed on CLL-monocytes while glycolytic parameters are found substantially reduced. (2.) In fact, glycolytic activity correlates positively with the monocytes’ ability to eliminate CLL-cells treated with anti-CD20 antibodies. (3.) PD-1/PD-L1 crosstalk leads to a reduced glycolytic and consequently phagocytic activity in monocytes. This interaction is targetable by modern ICP inhibitors.

Hypoxia-inducible factors (HiFs) are essential transcription factors for the cellular response to hypoxia. Expression and stabilization of HiFs can be triggered by hypoxia or by other factors under pathological stress such as inflammation and infection. While HiFs are known to be involved in T cell and macrophage activation, their functions in B lymphocytes are poorly defined.

Our work demonstrated that hypoxia-inducible factor-1α (HIF-1α) contributes to IL-10 production by B cells. HIF-1α regulates IL-10 transcription and HIF-1α-dependent glycolysis facilitates CD-1d<sup>hi</sup>CD5<sup>+</sup> B cell expansion. Mice with B cell-specific deletion of Hif1α have reduced number of IL-10-producing B cells, which result in an exacerbated collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE). Wild-type CD1d<sup>hi</sup>CD5<sup>+</sup> B cells, but not Hif1α-deficient CD1d<sup>hi</sup>CD5<sup>+</sup> B cells, protect recipient mice from autoimmune disease, while the protective function of Hif1α-deficient CD-1d<sup>hi</sup>CD5<sup>+</sup> B cells is restored when their defective IL-10 expression is genetically corrected.

Our study demonstrates the key function of the hypoxia-associated transcription factor HIF-1α in driving IL-10 expression in CD1d<sup>hi</sup>CD5<sup>+</sup> B cells, and in controlling their protective activity in autoimmune disease. Modulating the HIF-1α axis through pharmacologic agents may provide a tool to augment the immune regulatory potential of IL-10-producing B cells with the potential to prevent and/or treat systemic autoimmune inflammatory diseases.

Host-microbe interactions are considered a fundamental component influencing health and disease. Especially the gut microbiota and recently also their metabolites got into focus as potential modulators of their hosts’ immune responses. Among those metabolites derived from gut microbial fermentation of dietary fibers are the group of short chain fatty acids (SCFA). We have shown in the past that SCFA act as strong immunological mediators transmitting effects of the gut microbiota on allergies and systemic immune activation.

Because immune activation is intimately linked to bone homeostasis, we analyzed in this current project the effect of SCFA on bone. We investigated different mouse models addressing physiological bone homeostasis in naïve C57BL/6 and Rag1-/- mice as well as models for post-menopausal or inflammation-driven pathological bone loss during SCFA supplementation or fibre rich diets.

The analysis of tibial bone revealed that SCFA supplementation led to increased bone mass under physiological conditions. This was due to a direct impact on the metabolic status of osteoclast precursors, shifting it at early time points during differentiation to mature osteoclast towards enhanced glycolysis. Additionally, SCFA treatment was able to attenuate systemic bone loss in post-menopausal and inflammation-driven pathological bone loss.

These data suggest that microbial homeostasis in the gut associated with adequate production of SCFA is an important regulatory element in determining bone composition in mice. Therapeutic supplementation of SCFA or special diets rich in fibers to increase the endogenous production of SCFA may therefore provide a powerful instrument to balance osteoclast activity and prevent enhanced bone resorption.


Muesli every day can keep arthritis at bay
Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss

MARIO ZAISS
DEPARTMENT OF INTERNAL MEDICINE 3, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN
**PEOPLE**

**Prof. Dr. Gerhard Krönke**

Langener Wissenschaftspreis for Prof. Dr. med. Gerhard Krönke

For the second time in the last ten years, the renowned Langener Wissenschaftspreis, biannually awarded by the Paul Ehrlich Institute and the Stadtwerke Langen, went to a member of the Medical Immunology Campus Erlangen. In November 2017, Prof. Gerhard Krönke, Professor for Translational Immunology at the Department of Medicine 3, Universitätsklinikum Erlangen, received the Langener Wissenschaftspreis endowed with 15,000 euros for his outstanding research on the mechanisms of peripheral immune tolerance as base for the understanding and therapy of autoimmune diseases. Gerhard Krönke discovered a molecular mechanism that is comparable to ‘waste separation’. Tissue macrophages detect and safely dispose of dead cells belonging to the own body without any further effect. Inflammatory macrophages, however, detect and fight non-body pathogens by initiating an immune response and causing inflammation. Therefore, ideally, “self” and “foreign” waste can be processed separately. Gerhard Krönke focuses on the question of how the human immune system can differentiate between “self” and “foreign”. Wrong decisions of the immune system can lead to immune cells attacking the body’s own organs and tissues, which can lead to autoimmune diseases such as rheumatoid arthritis.

This research aims to elucidate different immune tolerance mechanisms of the body, which is a prerequisite for the development of new therapies for the treatment of autoimmune diseases.

Prof. Gerhard Krönke studied Medicine at the Medical University of Vienna from 1996 to 2002. Following his studies, Krönke worked at the Institute of Vascular Biology, University of Vienna and at the Cardiovascular Research Center of the University of Virginia, Charlottesville, USA. Since 2006, Krönke has been research group leader at the Department of Medicine 3 and has published numerous high-ranking publications and received an ERC starting grant.

**Prof. Dr. Thomas Gramberg**

Thiersch-Preis for Prof. Dr. Thomas Gramberg

Every year, on the occasion of the Dies Academicus, the FAU celebrates the day of its founding on November 4, 1743. As part of this celebration, the President of the FAU, Prof. Joachim Hornegger, hands over awards to scientists of the FAU, among others the Thiersch-Preis, an habilitation prize endowed with 1.500€. Last year’s awardee was Prof. Thomas Gramberg, Junior Professor of Antiviral Native Immunity at the Virology Institute, Universitätsklinikum Erlangen. The award was given to Prof. Gramberg for the discovery of the mechanism by which SAMHD1 acts as a retroviral infection restriction factor. In his habilitation thesis, Thomas Gramberg described the viral antagonist of SAMHD1, the accessory protein Vpx, and its interaction with SAMHD1 and elucidated the antiviral function of SAMHD1 by degrading viral DNA and thus blocking infection. These findings on SAMHD1 reveal possible targets for new antiretroviral drugs.

Prof. Gramberg studied biology at the FAU and did his doctorate in the laboratory of Prof. Dr. med. Stefan Pöhlmann at the Virology Institute, Universitätsklinikum Erlangen. After a postdoc period of three years in the laboratory of Prof. Nathaniel Landau at New York University, USA, he accepted the call for a junior professorship at the Virology Institute, where he has led an independent research group since 2010 to study the role of intracellular defense and detection mechanisms during viral infections.
Dr. Andrea Thoma-Kreß receives “Exploration Grant” of the Boehringer Ingelheim Foundation

The young scientist, Dr. Thoma-Kreß, head of the research group “Human T-Cell Leukemia Virus Type 1 (HTLV-1) and Adult T-Cell Leukemia” at the Virology Institute of the Universitätsklinikum Erlangen, successfully applied for the research fellowship “Exploration Grant” of the Boehringer Ingelheim Foundation. Her research project on “A novel positive feedback loop in viral onco-genesis: Regulation of the viral Tax oncoprotein by NF-κB” will be supported by the Boehringer Ingelheim Foundation with around 80,000 euros for the next 15 months. This grant is given to young scientists in the field of fundamental research to pursue new ideas and directions at an early career stage.

Andrea Thoma-Kreß studied Molecular Medicine at the FAU and after finishing her doctoral thesis in 2011, started her own independent research group at the Virology Institute.

Introducing our new members

Welcome Dr. Christian Lehmann

The Medical Immunology Campus Erlangen welcomes its new member Dr. rer. nat. Christian Lehmann, who leads his own research group in the laboratory of DC Biology (Prof. Diana Dudziak) in the Department of Dermatology, Universitätsklinikum Erlangen. Christian Lehmann studied Biomedical Chemistry at the Johannes Gutenberg University in Mainz and proceeded with his doctoral research and thesis at the lab of Prof. Diana Dudziak. The main research areas of Dr. Lehmann include tumor immunity, the role of dendritic cells in adaptive immune responses, vaccination strategies, Fc receptors and T cell responses.

Welcome Dr. Andreas Ramming

It is a pleasure to introduce our new member Dr. med. Andreas Ramming. Dr. Ramming studied Medicine at the FAU and finished his experimental doctoral thesis at the Department of Medicine 3 at the Universitätsklinikum Erlangen in the year 2010. After spending three years as resident and research fellow at the Rheumaerheinheit of the LMU Munich and at the Department of Rheumatology at the University Hospital Zurich, Switzerland, he returned to the Department of Medicine 3 in 2013 and started his own research group. Dr. Ramming is currently exploring the modulation of chronic inflammation and tissue repair in arthritis and fibrosis.

Welcome Dr. Ulrike Harre

The Medical Immunology Campus Erlangen would like to introduce its new member, Dr. rer. nat. Ulrike Harre, who, born in 1987, is our youngest member yet. Dr. Harre studied Biochemistry in Leipzig and, after spending one semester in a laboratory in Lyon, France, finished her doctorate at the Department of Medicine 3 of the Universitätsklinikum Erlangen in 2015. Dr. Harre’s research focuses on rheumatology and osteoimmunology with particular interest in the functional role of antibodies in triggering inflammation and tissue damage. Currently, she is working on the characterization of the mechanism of autoantibody effects on immune and bone cells.
UPCOMING EVENTS

Immunological Colloquium of the Medical Immunology Campus Erlangen – Summer 2018
Tuesdays, 5.15 pm

25.06.2018 (4 p.m.)
Dr. Joanne Reed
Garvan Institute of Medical Research, Sydney, Australia
Single cell analysis of self-reactive B cells in autoimmune disease

26.06.2018
Assoc. Prof. Daniel Christ
Garvan Institute of Medical Research, Sydney, Australia
Engineering antibody and T-cell specificity in vitro and in vivo

03.07.2018
Prof. Annemiek van Spriel
Department of Tumor Immunology, University of Nijmegen, Niederlande
Tetraspanins: molecular organizers of the immune cell surface

10.07.2018
Prof. Eyal Gottlieb
Technion – Israel Institute of Technology, Haifa, Israel
Identifying and exploiting cancer’s metabolic liabilities

Further Conferences and Events of Interest

September 2 – 5, 2018
5th European Congress of Immunology
Amsterdam
www.eci2018.org/home/

September 5 – 7, 2018
New Frontiers in Innate Immunity and Inflammation
Cluj-Napoca, Romania

September 6 – 8, 2018
26. Jahrestagung der Deutschen Gesellschaft für Immunogenetik
Freiburg
www.dgi2018.de/

September 16 – 20, 2018
NO2018 - 10th International Conference on the Biology, Chemistry and Therapeutic Applications of Nitric Oxide
Oxford
www.no2018.org.uk/

September 27 – 29, 2018
32th Annual Conference of the European Macrophage and Dendritic Cell Society
Verona
www.emdverona2018.com/

October 4 – 6, 2018
26th Annual Meeting of the Paul-Ehrlich-Society
Vienna

November 29 – December 1, 2018
ILC2018 – The 3rd International Conference on Innate Lymphoid Cells
Tokyo
www2.convention.co.jp/ilc2018/welcome.html

February 25 – 27, 2019
71st Annual Meeting of the German Society of Hygiene and Microbiology
Göttingen
www.dghm-kongress.de

Further Conferences and Events of Interest

June 27 – 29, 2018
International Conference on Immunology, Immunodeficiency and Immunotherapy 2018
Freiburg
www.uniklinik-freiburg.de/international-immunology.html

We are looking forward to suggestions for the next MICE newsletter.
Please send material to: Sonja.Poetzsch@uk-erlangen.de

Please note that the authors are responsible for the content of their contributions.

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Medical Immunology Campus Erlangen
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Dr. rer. nat. Sonja Pötzsch Scientific Coordinator

Microbiologisches Institut – Klinische Mikrobiologie, Immunologie und Hygiene
Universitätsklinikum Erlangen
Friedrich-Alexander-Universität
Erlangen-Nürnberg
Wasserturmstraße 3/5 · 91054 Erlangen
Phone +49.9131.85.225 71
Fax +49.9131.85.225 73
Mail Sonja.Poetzsch@uk-erlangen.de
www.mice.uni-erlangen.de

Conceptual Design and Editor
Dr. rer. nat. Sonja Pötzsch V.i.S.d.P.

Subscription via Email to:
Sonja.Poetzsch@uk-erlangen.de

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Please send material to:
Sonja.Poetzsch@uk-erlangen.de